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Aggressive variants of prostate cancer – Are we ready to apply specific treatment right now?

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ABSTRACT

Recently, adoption of novel drugs for systemic treatment of metastatic prostate cancer has led to a striking improvement of response rate and survival in both hormone-sensitive and castration-resistant disease. In most cases, prostate cancer essentially depends on androgen receptor signaling axis, even in castration-resistant setting, and hence may be targeted by second generation hormonal therapy. However, a subset of patients bears androgen-independent cancer biology with a short-term response to hormonal treatment, early and extensive visceral metastases, low PSA levels and poor outcomes. Identification and specific management of these rapidly fatal malignancies is of an unmet medical need since their classification and utilized therapeutic regimens vary significantly. Unfortunately, molecular pathways have not been sufficiently elucidated yet in order to provide an effective targeted treatment with a prolonged response. Lack of diagnostic and predictive biomarkers for these cancers makes successful counteractions against them even more sophisticated. In this comprehensive review, we aimed at summarizing the current body of literature reporting on causal molecular machinery as well as diagnostic and therapeutic concepts of aggressive prostate tumors and draw clinically relevant conclusions for the up-to-date sensible disease management.

Introduction

Prostate cancer (PC) is the second most common malignancy in the western world [1]. For many years, the mainstay treatment for metastatic PC has been androgen deprivation therapy (ADT) [2]. However, the therapeutic landscape of metastatic hormone-sensitive PC (mHSPC) has changed substantially over the past years, with significantly improved survival following early combination of ADT with docetaxel or abiraterone acetate [3,4]. Eventually, treatment resistance of PC cells will evolve until a castration-resistant stage is reached [5]. Interestingly, a substantial dependency on the androgen receptor (AR) signaling axis is present in castration-resistant PC (CRPC) setting, since secondary hormonal therapies based on enzalutamide, abiraterone acetate and apalutamide have achieved prolonged survival in CRPC

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patients [6–8].

In contrast, a subset of patients with a metastatic (m)CRPC will express an androgen-independent phenotype with a clinical appearance of a limited response to ADT, early and extensive visceral metastases, relatively low PSA levels and significantly worse cancer-specific (CSS) and overall survival (OS). Based on these typical clinical features, this subgroup has been summarized as "aggressive variants of prostate cancer" (AVPC) [9].

Even though these aggressive PC cells are mostly dedifferentiated (also referred to as "anaplastic PC" [10]), expression of neuroendocrine (NE) features is frequently observed. While de-novo neuroendocrine prostate cancer (NEPC) is rare [11], NE transdifferentiation during increasingly potent treatment of advanced PC, the so-called treatment-emergent (t)NEPC, is by far more common. Based on the SEER database, the age-adjusted incidence of NEPC increased about 6.8% per year between 2004 and 2011 [12].

Identification of AVPC has clinical implications since response rates for standard taxane-based chemo-hormonal therapy are low [13] and more sophisticated platinum-based combination therapies have been recommended [10]. In the contemporary review, clinical and molecular features of AVPC are being reviewed in accordance to previous publications [14,15]. In addition, evidence regarding therapeutic options for AVPC and relevant implications for practical disease management are highlighted.

Defining the disease

Initially, the term "NEPC" was preferably used to describe aggressive PC. Since the original World Health Organization (WHO) definition of NEPC was based on classifications from NE cancers in other organs and did not take into account prostate-specific pathological aspects, the Prostate Cancer Foundation introduced a morphological classification of NEPC that is currently regarded as a standard in many centers. The updated classification defined the following subtypes: (I) usual prostate adenocarcinoma (Adeno-PC) with neuroendocrine differentiation: (II) Adeno-PC with Paneth cell NE differentiation; (III) carcinoid tumor; (IV) small cell prostatic carcinoma (SCPC); (V) large cell NEPC; (VI) mixed NE carcinoma – acinar Adeno-PC. Moreover, the authors defined t-NEPC as an independent entity [16].

In addition to this morphology-based nomenclature, further classifications focus on the aggressive clinical course and are based on clinical rather than histomorphological features. Consequently, terms such as "anaplastic PC" [10] and AVPC [9] are equally used and it has been recognized that these terms are not restricted to the variants that have been described by The Prostate Cancer Foundation consensus group but include a broad spectrum of AR-independent mCRPC [17]. However, it has been debated whether distinguishing between AVPC and t-NEPC has subsequent clinical implications [15]. A distinguished definition of AVPC or anaplastic PC has recently been introduced by Aparicio et al. [10]. Hereby the authors proposed seven clinical criteria, at least one of which had to be present to fulfill "anaplastic" criteria: (I) any histologic evidence of SCPC; (II) exclusively visceral metastases; (III) radiographically predominant lytic bone metastases diagnosed by x-ray or CT scan; (IV) bulky lymphadenopathy or bulky ($\geq$5 cm, respectively) high-grade (Gleason $\geq$ 8) tumor mass in prostate/pelvis; (V) Low PSA level ($\leq$10 ng/mL) at initial presentation (prior to ADT or at symptomatic progression in the castrate setting) and high volume ($\geq$20) bone metastases; (VI) presence of neuroendocrine markers on histology (positive staining for chromogranin A (CGA), synaptophysin (SYP) or elevated serum levels of CGA, gastrin releasing peptide (GRP) (both features had to be combined with either elevated lactate dehydrogenase (LDH) serum levels, malignant hypercalcemia, or elevated serum carcinoembryonic antigen (CEA) (all in absence of other causes); (VII) short interval ($\leq$6 months) to androgen-independent progression following the initiation of ADT. Notably, presence of these features in mHSPC disease has been recently demonstrated to convey inferior outcomes as well [18].

Molecular alterations

Primary anaplastic variants of prostate cancer

Unusual primary histological variants account for ~10% of prostate cancers [19]. The most frequently found in clinical practice are: NEPC, ductal Adeno-PC, sarcomatoid (carcinosarcoma), basal cell, squamous cell, adenosquamous and urothelial carcinoma [20]. In this article, we will discuss mainly the NE variant. NE cells can only be determined by immunohistochemical (IHC) analysis (ie, synaptophysin (SYP), CD56, chromogranin (CGA) and neuron specific enolase (NSE)).

At the molecular level, these NE tumors present with RB1/PTEN losses and TP53 mutations or deficiencies, which have been associated with androgen independence as well as increased expression/activity of aurora kinase A and N-Myc [21–23]. These cells are present also in the normal prostate and can increase the aggressiveness of Adeno-PC through the inhibition of apoptosis and stimulation of neoangiogenesis [24–26]. Although several papers have shown a relation between the amount of NE cells present in the prostate with treatment response and evolution to castration resistant Adeno-PC, currently there are no recommendations for a routine use of IHC staining of prostate biopsy samples [27–30].

Paneth cell – like NE differentiation represents a distinctive subset of eosinophilic NE cells which can be seen as either patchy isolated cells or diffusely between glands and nests of Adeno-PC [31]. These cells are diffusely positive for NE markers and have a low proliferation rate [16]. This subset has often been classified as the Gleason pattern 5, although some authors emphasized that applying the Gleason score to these foci does not accurately reflect their clinical behavior and generally favorable prognosis [32,33]. Until the prognostic value will be established, the clinical significance of this histological subtype of NE differentiation remains unknown.

Pure SCPC is very rare and often diagnosed as metastasized disease. Most common histological form presents a mixed SCPC and Adeno-PC, while the acinar component varies in grade and extent [34]. On IHC staining, SCPC can be positive for at least one NE marker such as SYP or CGA and negative for AR and PSA [35]. Due to the rarity of primary SCPC, this diagnosis should be stated after exclusion of metastasis in the prostate for other sites or direct invasion from the bladder. On both protein level by fluorescence in situ hybridization (FISH) and on mRNA level by reverse transcription polymerase chain reaction (RT-PCR), it can be distinguished between small cell carcinoma of the bladder and prostate since the latter is positive for TMPRSS2-ERG gene fusion [36,37].

In contrast to SCPC, carcinoid tumors derived from the prostate are well-differentiated NE malignancies that do not express any components or markers for Adeno-PC and present a relatively good prognosis after treatment [11,38]. However, there are only 5 pure cases of carcinoid tumor described in the literature and a differential diagnosis to metastasis from a gastrointestinal cancers is mandatory [16].

Treatment derived neuroendocrine and small cell prostate cancer

Neuroendocrine prostate cancer

Adeno-PC can undergo transformation into NE cells and develop into tNEPC, typical properties of which are the terminal differentiation as well as the lack of proliferating features – such as Ki-67 expression [39]. In recent years, it has become evident that androgen depletion is a major driver of NE differentiation (NED) as transdifferentiation from an epithelial-like phenotype to a NE-like phenotype induced by hormonal treatment. Indeed, many preclinical and clinical studies were able to show that long term androgen exposure is associated with a NED [40,41] mediated by different mechanisms like regulation via the receptor protein tyrosine phosphatase a (RPTPa)- mediated signalling

Autor	Study design	Number treated	Cohort	Regimen	Outcomes	Tox. Grad 3-4
Amato et al., J Urol, 1992	retrospective	21	62% SCPC 38% mixed	Cis/Eto ± Dox or Vin/Dox/Cyc	RR 62% S 9.4m	not reported
Papandreou et al., J Clin Oncol, 2002	prospective, single-arm	36	67% small cell 33% mixed	Cis/Eto/Dox	RR 61% TTP 5.8m S 10.5m	100% neutropenia 68% infection 66 % thrombocytopenia
Steineck et al., Acta Oncol, 2002	retrospective	30	30% SCPC 43% anaplastic 13% mixed	Cis or Car + Eto/Est	RR 50% S(range) 8-941d	77% neutropenia 40% thrombocytopenia
Asmis et al., BJU Int, 2006	retrospective	10	50% SCPC 50% mixed	Cis or Car + Eto (7 patients)	S 9.5m	not reported
Culine et al., J Urol, 2007	prospective	41	CRPC + sNE markers	Cis/Doc	RR 41% S 12m	35% of courses with neutropenia
Flechon et al., Ann Oncol, 2011	prospective	55	CRPC + M(visceral) a/o sNE markers	Car/Eto	RR 8.9% PFS 2.9m S 9.6m	66% neutropenia 33% thrombocytopenia 27% anemia
Aparicio et al., Clin Cancer Res, 2013	prospective, single-arm	113	cAVPC	1.line: Car/Doc 2.line: Cis/Eto	TTP1 5.1m TTP2 3.0m S 16m	2.7% febrile neutropenia 1.8% thrombosis
Corn et al., J Clin Oncol, 2015 Aparicio et al., J Clin Oncol, 2017	prospective, 1:1 randomized	160	CRPC, stratified for cAVPC	Car/Cab vs. Cab	PFS (all) 7.4m vs. 4.6m PFS (cAVPC) 5.6m vs. 3.8m	15% vs. 4% neutropenia 17% vs. 2% anemia 8% vs. 0% thrombocytopenia
Beltran et al., Clin Cancer Res, 2018	prospective, single-arm	60	SCPC a/o adeno-PC+IHC for NE markers a/o liver M+ w/o PSA a/o sNE markers	Alisertib	PF at 6 m 13.4% S 9.5m	13% neutropenia 10% fatigue 10% GI
Apostolidis et al., Oncotarget, 2019	retrospective	46	45.7% SCPC 43.5% mixed	Car or Cis + Eto (n=27)	RR (Car/Eto or Cis/Eto) 48.1% PFS (n=34 with systemic therapy) 6.6 mos. OS 15.5 mos.	not reported

Fig. 1. Selected studies on systemic treatment of metastatic aggressive variants of prostate cancer. *SCPC:* small cell prostate cancer; *CRPC:* castration-resistant prostate cancer; *Cis:* cisplatin; *Eto:* etoposide; *Dox:* doxorubicin; *Vin:* vincristine; *Cyc:* cyclophosphamide; *Car:* carboplatin; *Est:* estramustine; *Doc:* docetaxel, M: metastasis; *(s)NE:* (serum) neuroendocrine; *(c)AVPC:* (clinical) aggressive variants of prostate cancer; *GI:* gastrointestinal; *PC:* prostate cancer; *IHC:* immunohistochemistry; *RR:* response rate; *S:* survival; *TTP:* time to progression; *PF(S):* progression-free (survival); *m:* months; *d:* days; *Tox.:* toxicities.

pathway, the PTP1B-mediated signalling pathway or the protocadherin-PC (PCDH-PC)-mediated signalling pathway (reviewed in [42]). Besides these pathways, ERK/MAPK activation plays a critical role in converging multiple signaling pathways for NED in PC cells as well [43]. Although its molecular pathogenesis remains not fully understood, it appears that NED requires TP53 and RB1 aberration. Thus, Akamatsu et al. modeled the development of NEPC cells from conventional Adeno-PC using a patient-derived xenograft and found that the placental gene PEG10 is depressed during the adaptive response to androgen receptor interference and subsequently highly upregulated in NEPC. Moreover, the authors of this study demonstrated that both the androgen receptor and the E2F/RB pathway dynamically regulate distinct post-transcriptional and post-translational isoforms of PEG10. In addition, PEG10 promotes cell-cycle progression from G0/G1 via of TP53 loss [44]. These findings again show the mechanistic relevance of RB1 and TP53 loss in NEPC cells and suggest PEG10 as a specific target for future therapies. Interestingly, de Leeuw et al. demonstrated an enhanced response to cabazitaxel in Rb1-depleted *in vitro* and xenograft models [45].

There is evidence that high intracellular cAMP levels lead to NED of PC cells. Furthermore, cytocine Interleukin-6 is an important inducer of NED of PC cells probably mediated by the transcription factor STAT3 (reviewed in [42]). Recently, Li and co-workers performed whole-transcriptome sequencing of prostate tumors in order to investigate the development of NEPC as well as identify its driver genes and figure out potential treatment options for NEPC prevention including 27 Adeno-PC and five NEPC patients' samples. Thereby, they were able to identify a NEPC-specific RNA splicing signature that is predominantly controlled by serine/arginine repetitive matrix 4 (SRRM4), thus underlining the fact that SRRM4 drives NEPC progression and proposing SRRM4 as a potential therapeutic target for NEPC [46].

Small cell prostatic carcinoma

In general, SCPC cells are positive for synaptophysin, chromogranin, NSE and CD56 [43,47]. SCPC can either emerge de novo or in the setting of castrate resistant Adeno-PC as there is clear evidence for SCPC being significantly more common in men with CRPC after exposure to ADT [48,49]. Biologically, it has been suggested that certain stem cells can differentiate into both Adeno-PC and SCPC rather than fully differentiated Adeno-PC cells dedifferentiating into SCPC [50]. On

the other hand, in patients treated with ADT, development of SCPC might be an escape mechanism of a subpopulation of hormone-independent cells resulting from the selective pressure of hormonal therapy (reviewed in [47]). Furthermore it has been reported that in benign prostate as well as Adeno-PC, the Interleucin-8-CXCR2-P53 pathway provides a strong growth inhibitory signal that keeps NE cells quiescent [51]. P53 mutation- a result of environmental pressure from hormonal therapy, inactivates this pathway consequently leading to hyperproliferation and aggressive behavior of the NE cells, resulting in the development of SCPC [51]. Another preclinal study showed that exposure of AR-positive LNCaP cells to a hormone deficient medium drastically increased cyclic AMP production and this may identify the biochemical pathway through which hormone depletion induces a NE conversion of PC cells [52]. In this context, Wang et al. assessed 61 SCPC patients and found that high AR gene copy number emerges during the development of SCPC, often in association with TMPRSS2-ERG rearrangement [53].

To summarize, there is strong evidence that hormonal therapy is able to transform Adeno-PC to more aggressive variants including SCPC and NEPC. Although many causal pathways have been proposed, exact molecular mechanisms have still to be elucidated more profoundly.

Clinical implications

Therapeutic management of histologically defined pure or with adeno-PC mixed NEPC or clinically and/or molecularly classified AVPC, sharing clinical features with NEPC, historically relies on platinum-based regimens since doublet cytotoxic combination of cisplatin and etoposide has proven strikingly efficacious and become treatment of choice for small cell lung cancer (SCLC) in the 1980s [54]. In addition, particularly anaplastic forms of NEC of different origins have been shown to exhibit a considerable response to this combination [55]. Originally, Moore et al. identified 50 cases with a SCPC from their own institution or published as case reports from elsewhere between 1977 and 1992 [56]. Four patients without treatment deceased after only 2.8 months (mos.), while none of another five men receiving hormonal therapy really responded demonstrating an average time to disease progression and death of 6.1 and 6.9 mos., respectively, and underscoring the hormonal unresponsiveness of SCPC. Although being very heterogeneous at that time, chemotherapy provided an average survival of about 12 mos., hence favoring its early utilization during disease course.

Hereinafter, increasing clinical interest in AVPC resulted in a number of trials, most relevant of which are summarized in Fig. 1 [10,13,57–63]. Amato et al. reported retrospectively of 21 metastatic SCPC patients treated with cisplatin and etoposide ± doxorubicin or vincristine, doxorubicin and cyclophosphamide, following either hormonal therapy or as initial regimen, resulting in a response rate and survival of 62% and 9.4 mos., respectively [58]. Of note, 62% had a pure SCPC and 38% a mixed histology of adeno- and SCPC. Importantly, PSA or PAP elevation was uncommon (7% and 10%, respectively), while CEA rise was observed in 62%. The authors also argued for early induction of chemotherapy in the disease management.

The first prospective data emerged from the M.D. Anderson Cancer Center after the turn of the millennium. Papandreou et al. treated patients with histologically proven pure or mixed SCPC, 81% of whom had been pretreated by hormonal therapy, with 4 cycles of cisplatin, etoposide and doxorubicin without primary support with granulocyte colony-stimulating factors (G-CSFs). Response rate, time to progression and overall survival were 61%, 5.8 mos. and 10.5 mos., respectively [62]. This regimen was accompanied by grade 3–4 neutropenia (100%), thrombocytopenia (66%), mucositis (21%) and infection (68%), whereas 3/36 men died of toxicities. Importantly, there was no survival benefit of adding doxorubicin to cisplatin + etoposide but a menacing toxicity rate. Drop of PSA and CEA, elevated to a different extent before therapy, corresponded to clinical response in some cases.

In another prospective phase II trial, Culine et al. treated 41 men with mCRPC and supranormal serum NSE and/or CGA with 6 cycles of cisplatin + docetaxel hence targeting both putatively existing neuroendocrine and hormone-independent adenocarcinoma clones [13]. G-CSF support was administered in patients at risk or following febrile neutropenia. A 50%-decrease of NSE and/or CGA was observed in 33% of cases, while PSA response was 48%. Response rate and survival were 41% and 12 mos., while grade 3–4 neutropenia occurred in 35% of courses and one man died of toxicity. In this study, no histological confirmation of present NEPC clones before treatment has been performed paving the way for the concept of clinically defining AVPC.

The French GETUG P01 trial used clinical criteria for patient selection as well as targeting of predominantly neuroendocrine pathway. 55 patients with mCRPC and visceral metastases and/or NSE and/or CGA elevation were given up to 6x carboplatin + etoposide without primary application of G-CSFs [61]. Objective, NSE, CGA and PSA response rates were 8.9%, 31%, 7% and 8%. PFS and OS were 2.9 mos. and 9.6 mos., respectively. Most common grade 3–4 toxicities were neutropenia (65.5%), thrombocytopenia (32.7%) and anemia (27.3%) besides one toxicity-related death.

Two largest clinical studies originate from the M.D. Anderson Cancer Center. Aparicio et al. treated 113 patients fulfilling the aforementioned clinical AVPC criteria with at least 4x carboplatin and docetaxel in the first-line setting, followed by 4x cisplatin and etoposide upon progression [10]. Only patients with histologically confirmed SCPC were not required to have received ADT. In addition, G-CSF support was at discretion of the treating physician. Serum concentration of at least 1 out of 6 neuroendocrine markers (CGA, calcitonin, somatostatin, ACTH, ADH and gastrin-releasing peptide) was augmented at baseline. Time to the first and second progression as well as survival were 5.1 mos., 3.0 mos. and 16 mos., respectively, whereas bulky disease and serum calcitonin predicted for both poorer OS and PFS. Febrile neutropenia was the most common hematologic toxicity (2.7%), one patient died of neutropenic sepsis. Subsequent trial (NCT01505868) randomized 160 mCRPC patients to receive up to 10 cycles of either carboplatin + cabazitaxel or cabazitaxel alone with primary G-CSF prophylaxis, stratifying participants upon clinical AVPC (cAVPC) criteria (slightly over 50%) [60,64]. Safety was reported after accrual of 93% of men, while carboplatin + cabazitaxel yielded more grade 3–4 adverse events than cabazitaxel monotherapy (neutropenia 15% vs. 4%, anemia 17% vs. 2%, thrombocytopenia 8% vs. 0%) [60]. Compared to monotherapy cohort, progression-free survival was significantly extended in the combination arm in the overall population (7.4 mos. vs. 4.6 mos.) as well in the cohorts fulfilling cAVPC (combination vs. monotherapy: n = 45 vs. n = 41) and mAVPC (combination vs. monotherapy: n = 20 vs. n = 7) criteria (5.6 mos. vs. 3.8 mos.; 8.0 mos. vs. 1.7 mos., respectively) [64]. On the contrary, patients without cAVPC or mAVPC demonstrated a non-significant trend in favor of the combination.

Notably, contemporary trial by Beltran et al. focused on inhibiting of N-myc signaling as an important pathway driving NEPC progression by targeting its stabilizing factor cell-cycle kinase Aurora kinase A (AURKA) with the drug alisertib [59]. 60 males with mCRPC exhibiting at least one of the following criteria were enrolled: histologically small-cell NEPC, adeno-PC with > 50% IHC staining for NE markers, emergence of liver metastasis without PSA progression and augmented serum CGA and/or NSE. A pretreatment metastatic biopsy was carried out. Serum NSE, CGA and CEA were elevated to a varying extent, median PSA was normal. Genomic alterations included RB1 (55%), TP53 (46%), BRCA2 (29%) and AR (27%). Given the rate of 13.4% of men being radiographically progression-free at 6 mos., the study dismissed the alternative hypothesis (radiographical progression-free rate at 6 mos. ≥ 30%), thus missing its primary endpoint. Overall survival was 9.5 mos., while some individuals suggestive of N-myc and AURKA overactivity experienced sustainable clinical advantage. Grade 3–4 toxicities included neutropenia (13%), thrombocytopenia (5%), fatigue

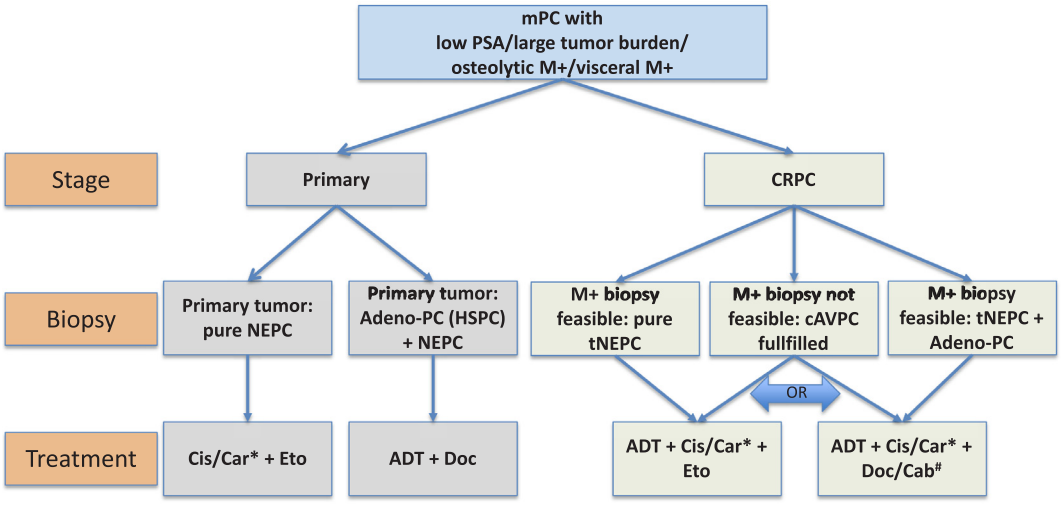

Fig. 2. Diagnostic and treatment algorithm of AVPC. *mPC:* metastasized prostate cancer; *M+:* metastasis; *HSPC:* hormone-sensitive prostate cancer; *Adeno-PC:* adenocarcinoma of the prostate; *CRPC:* castration-resistant prostate cancer; *(t)NEPC:* (treatment-emerging) neuroendocrine prostate cancer; *ADT:* androgen deprivation therapy; *Cis:* cisplatin; *Car:* carboplatin; *Eto:* etoposide; *Doc:* docetaxel; *Cab:* cabazitaxel; *PS:* performance status; *cAVPC:* clinical criteria for aggressive variants of prostate cancer.

(10%), gastrointestinal events (10%) and dehydration (5%).

Most recently, Apostolidis and collaborators reported in their retrospective trial on clinical characteristics and treatment outcomes of 46 patients with NEPC treated over a 17-year period at two German high-volume centers [65]. Of note, 39.1% were initially diagnosed with adeno-PC and 43.5% presented a mixed histology at NEPC diagnosis. 58.7% received platinum and etoposide with a response rate of 48.1% in the first-line setting. Overall, OS from NEPC diagnosis was 15.5 mos., while PFS for 73.9% of men who received first-line systemic therapy was 6.6 mos. Interestingly, solely prior adeno-PC predicted for a poorer OS, whereas no survival disadvantage was conferred by the presence of a mixed histology as well as elevation of serum PSA, NSE and CGA.

Taken together, considerable progress has been achieved in identifying patients with particularly aggressive tumor behavior requiring sophisticated management in recent years.

Unfortunately, response rates and survival are still modest, while current evidence is limited by a small sample size and number of prospective clinical trials, heterogeneous definitions and mixed tumor biology of AVPC patients enrolled as well as still emerging but not yet established molecular or genetic profiling of NEPC. In addition, individuals were exposed to varying systemic therapies before being enrolled in these studies, translating in presumably different patterns of resistance mechanisms.

Another unsolved clinical conundrum is a shortcoming of prospectively and consequently assessed prognostic and above all predictive markers for AVPC. This tempers the current practical relevance of NE serum markers as well, since even the cut-off values for abnormal readings of NSE and CGA were completely different in the studies of Beltran et al. and Flechon et al. [59,61]. It is noteworthy that neither NSE nor CGA elevation were associated with worse OS in the study of Apostolodis and co-workers [65]. Furthermore, in the study of Aparicio and colleagues, serum levels of calcitonin but not of CGA were associated with worse PFS and OS, suggesting that markers other than CGA, or a combination of NE markers, might show stronger associations and facilitate better identifying of distinct phenotypes [10].

Beside molecular biomarkers, the proper selection of imaging methods for AVPC will be challenging in the future. For instance, NE tumors are characterized by overexpression of somatostatin receptors, making positron emission tomography/computed tomography (PET/CT) with ^{68}Gallium (^{68}Ga)-labeled somatostatin analogues a promising modality for imaging of these malignancies including NEPC [66]. Chen et al. described a case of prostate cancer exhibiting a lesion in prostate gland with the highest Ga-PSMA uptake yet being strongly avid for Ga-DOTATOC, suggesting NED [67]. After hormonal therapy, PSA decreased but CGA elevation portended progression of NE cells. In a recent case report, ^{68}Ga-DOTA NOC PET-CT detected ^{68}Ga-PSMA negative metastases of NEPC [67,68]. It is still to be elucidated in the future how these advances in molecular imaging can sensibly impact the clinical management of AVPC.

Further scientific and clinical efforts are warranted to better select patients harboring AVPC to receive specific and efficacious treatment. In this context, several ongoing trials focus on systemic therapy of AVPC. NCT03263650 is a randomized phase 2 trials from the M.D. Anderson group assessing olaparib maintenance following cabazitaxel + carboplatin induction chemotherapy in men with cAVPC or mAVPC. Another phase II trial called PICK-NEPC (NCT03179410) investigates the potential of the PD-L1 inhibitor avelumab to treat NEPC. Last not least, males with NEPC or NE urothelial cancers are being enrolled in a phase 1b trial (NCT03582475) to receive the PD-1 blocker pembrolizumab in combination with etoposide + cis-/carboplatin or etoposide + carboplatin + docetaxel.

Are we ready to apply specific treatment right now? It is still challenging to identify AVPC patients in the clinical routine outside of specialized centers for molecular/genetic profiling and, in particular, select the right disease stage to sensibly utilize specific treatment concepts. Currently, cisplatin or carboplatin combined with etoposide without ADT but with G-CSF support represents the most appropriate and aggressive treatment option for males with a metastatic pure NEPC that has the most aggressive biologic behavior and poor outcomes [17] (Fig. 2). In case of a metastatic adeno-PC with a partial NE differentiation in the stage of mHSPC, commencing ADT + docetaxel appears to be a reasonable option since hormone-sensitive adeno-PC clones are targeted by ADT, while hormone-insensitive ones and NE clones are assailed by docetaxel which has been shown to be modestly active in

SCLC [69,70]. For treatment-emerging NEPC mostly co-existing with adeno-PC clones and having been previously pretreated with at least ADT, either cis-/carboplatin + etoposide or cis-/carboplatin + taxane accompanied by G-CSF and ADT administration should be utilized. It is however unclear, which proportion of NEPC represents the threshold to favor the first over the second strategy.

Conclusions

AVPC represent a clinically and biologically heterogeneous entity of tumors which often share at least a partial component of NE differentiation. NE component is rarely present during primary diagnosis of mHSPC, but frequently induced by long-term AR pathway targeting therapy. If feasible, metastatic lesion biopsy should be performed in males with metastastatic PC suspicious for AVPC in order to more reliably tailor treatment. Current body of literature provides a strong evidence favoring platinum/etoposide-based therapy for a pure mSCPC. In case of a mixed adeno-PC and NEPC, combination of ADT and docetaxel could be proposed aiming at targeting each pathology component. At the mCRPC stage, patients with tNEPC benefit from a combination of continuous ADT, and platinum-based therapy combined with etoposide or taxane. Molecular-based signatures and useful markers are still lacking to improve the treatment decision-making and to propose a clear distinction between these two options in routine practice. On the whole, treatment centralization of these sophisticated disease forms currently appears preferential for optimizing outcomes.

Conflict of interest statement

The authors declared that there is no conflict of interest.

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