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ORIGINAL ARTICLE

Real-world experience in treatment outcome and genomic insights for metastatic prostate neuroendocrine carcinoma

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Abstract

Background: Neuroendocrine prostate cancer (NEPC) (de novo or treatment-related [t-NEPC]) is a rare and deadly variant of prostate cancer. While de novo NEPC is rare, t-NEPC occurs more frequently in patients with castration-refractory prostate cancer. Owing to the rarity of NEPC, no standard treatment has been established, and the outcomes are generally unsatisfactory.

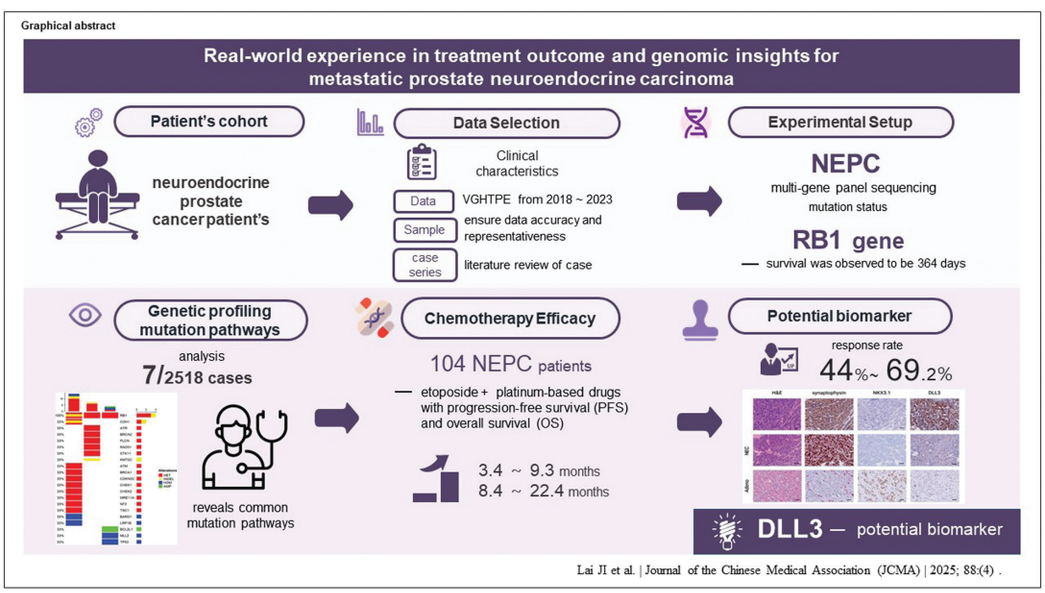
Methods: This study retrospectively reviewed NEPC cases at Taipei Veterans General Hospital between 2018 and 2023. Clinical outcomes, treatment modalities, and related genomic profiles were recorded. We also performed a literature review of case series reporting the outcomes of chemotherapeutic regimens for NEPC.

Results: From 2158 cases of prostate cancer cases diagnosed during the study period, only 7 had pathologically proven NEPC (0.3%), and the median overall survival was 364 days. Three patients who underwent multigene panel sequencing had mutations in *RB1*, and delta-like ligand 3 (DLL3) immunohistochemical staining showed a positivity rate of 50%. We performed a literature review on chemotherapy outcomes in patients with NEPC. In six studies with 104 patients, etoposide + platinum treatment was most commonly used. The progression-free survival (PFS) and overall survival ranged from 3.4 to 9.3 and 8.4 to 22.4 months, respectively. The response rates ranged from 44% to 69.2%. These studies were consistent with a dismal overall survival rate, despite a high response rate to the initial chemotherapy regimen.

Conclusion: Our study reported poor outcomes with chemotherapy, with a high frequency of retinoblastoma protein (RB) loss and DLL3 positivity. Further clinical developments targeting DLL3 are warranted.

Keywords: DLL3; Neuroendocrine; Prostate cancer

Graphical abstract



1. INTRODUCTION

Prostate cancer ranks second among all cancer diagnoses worldwide, and is a leading cause of cancer-related mortality. Most prostate cancer cases comprise an adenocarcinoma cell type, whereas rare pathological subtypes such as sarcomatoid or neuroendocrine prostate cancer (NEPC) occur in <2% of cases.[1] Prostate adenocarcinoma strongly depends on androgen signaling, which forms the basis of androgen deprivation therapy (ADT).[2] The current standard treatments for advanced prostate adenocarcinoma include ADT, novel hormonal agents (NHA), radium-223, taxane-based chemotherapy, and lutetium-prostate-specific membrane antigen (PSMA) radioligand therapy.[3] NEPC represents a rare entity that is currently considered to be androgen independent, and typically manifests with the downregulation of androgen receptor (AR), prostate-specific antigen (PSA), and PSMA expression,[4] with rapid clinical progression, and unsatisfactory response to treatment[4]; thus, it represents an unmet need for patients.

The etiology of NEPC is controversially heterogeneous, and is classified into de novo and treatment-related NEPC (t-NEPC), according to the origin of carcinogenesis. De novo NEPC comprises <1% of all prostate cancers,[5] whereas t-NEPC has an incidence of 15% to 20% in patients with castration-refractory prostate cancer (CPRC) after ADT and/or NHA treatment.[6] Transcriptomic profiling of t-NEPC samples demonstrated low frequencies of DNA damage pathway gene mutations,[6] suggesting a pattern distinct from the high prevalence (~30%) of homologous repair gene (*HRR*) mutations in prostate adenocarcinoma, although higher rates have been reported for de novo NEPC.[7]

Owing to its extremely low prevalence, large-scale clinical studies on advanced NEPC treatment are limited, and therapeutic approaches follow the guidelines for small-cell lung cancer (SCLC).[8] Generally, platinum-based chemotherapy is preferred, with the etoposide + platinum (EP) combination being frequently used, which is supported by a retrospective study of 87 patients reporting that most patients received an EP combination.[4,9,10] This study illustrated the poor clinical outcomes of chemotherapy, with a median progression-free survival (PFS) of approximately 5 months, and reported significantly better survival outcomes for t-NEPC than for de novo NEPC.[10] Although a small study reported 41% PD-L1 positivity in NEPC,[11] clinical studies of immune checkpoint inhibitors have shown low response rates.[12,13] Additionally, targeted therapy with aurora kinase A inhibitors has shown unsatisfactory results in a phase 2 trial.[14] Currently, novel therapies, including EZH2 inhibitors,[15] CEACAM5 antibody drug conjugates,[16] and other targeted therapies, are being actively investigated.

Delta-like ligand 3 (DLL3) is a novel therapeutic target for neuroendocrine tumors. DLL3 is a ligand of the Notch pathway[17] that is associated with the chemotherapy response in neuroendocrine lung cancers.[18] DLL3 targeting agents have shown promising results in phase 2 trials of SCLC.[19] However, data on DLL3 expression in NEPC are extremely limited. A recent study reported a 75% DLL3 positive rate in patients with NEPC,[20] and with the presence of DLL3 being associated with poor outcomes. With the rapid progression of DLL3 targeting agents, the question of whether such agents are active in DLL3-positive NEPC has become clinically important, and warrants further investigation.

Here, we report a retrospective analysis of patients with NEPC who were diagnosed and treated at our institution. We focused on treatment outcomes, specific regimens, and genomic features, if available. DLL3 expression in patient samples was also assessed. The clinical and genomic data from the case series documented in this present study provide important insights into this rare but deadly cancer type.

2. METHODS

2.1. Literature review

We screened for case series published in PubMed before December 2023, and their related details are described in Supplementary File 1, http://links.lww.com/JCMA/A307.

2.2. Clinical analysis of treatment outcome and clinical characteristics of patients with prostate neuroendocrine carcinoma

We retrospectively studied the clinical data of patients diagnosed with NEPC at the Taipei Veterans General Hospital. Cases of interest were identified from medical records. This study was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (IRB approval number: 2023-03-006CC). The details are provided in Supplementary File 1, http://links.lww.com/JCMA/A307.

2.3. Multigene panel testing for mutation status

Two patients received multigene panel testing using the ACTOnco®+ panel (https://www.actgenomics.com/tests-professional/actonco), and one patient underwent the Foundation One CDx panel (https://www.foundationmedicine.com/test/foundationone-cdx). The mutation landscape oncoprint was drawn using the R package "ComplexHeatmap."

2.4. Histology and immunostaining

Detailed immunostaining methods are described in Supplementary File 1, http://links.lww.com/JCMA/A307.

3. RESULTS

3.1. Clinical characteristics of NEPC in the Veterans General Hospital, Taipei (VGHTPE) cohort

All patients diagnosed with prostate cancer between January 1, 2018 and January 1, 2023 were retrospectively analyzed (Fig. 1A). In total, 2158 patients were diagnosed with prostate cancer, of which seven patients were diagnosed with NEPC (0.3%; Table 1). One patient was lost to follow-up 1 month post-diagnosis and was, therefore, excluded. In the six patients analyzed, the median age was 73 years (range: 68-91 years; Fig. 1B). Five of six patients were diagnosed with mixed adenocarcinoma and NEPC, and their median overall survival (OS) post-diagnosis was 361 days (range, 79-1366 days; Fig. 1C). The median initial PSA level was 8.9 ng/mL (range: 3.2-163 ng/mL) in patients with mixed adenocarcinoma and NEPC; in two patients with only NEPC, the PSA were 0.04 and 0.33,

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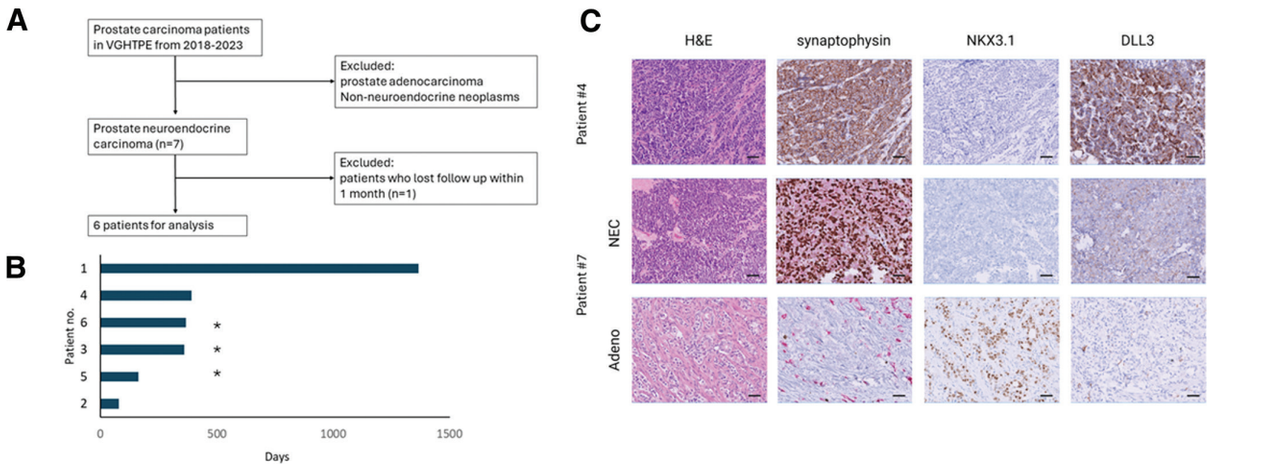

Fig. 1 A, Flowchart of case selection for clinical analysis of NEPC. B, Swimmer plot of overall survival. Asterisk denotes patient with positive staining for DLL3. C, Pathological immunohistochemistry staining for representative patients. Adeno = prostate adenocarcinoma; DLL3 = delta-like ligand 3; NEC = neuroendocrine prostate cancer.

Table 1

Clinical characteristics of our cohort

No.	Pathology	Age	Initial PSA	Recurrent/de novo	Metastasis sites	1st line chemotherapy	1st line PFS, d	OS	DLL3
1	adeno + NEC	78	42	de novo	bone, abdominal lymph node	docetaxel/carboplatin	1366	1366	negative
2	adeno + NEC	91	15.5	de novo	bone, abdominal lymph node	none	N/A	79	negative
3	adeno + NEC	73	8.9	de novo	bone, retroperitoneal lymph node	cisplatin/etoposide	208	361	positive
4	adeno + NEC	68	163	de novo	bone, retroperitoneal lymph node	none	N/A	392	negative
5	NEC	68	0.04	recurrent	bone	cisplatin/etoposide	82	163	positive
6	adeno + NEC	71	3.2	de novo	bone, abdominal lymph node	cisplatin/etoposide	93	367	positive

adeno = adenocarcinoma; NA = not available; NEC = neuroendocrine carcinoma; PFS = progression-free survival (in days); OS = overall survival (in days).

respectively. These five patients presented with stage IV disease at initial diagnosis, with only one patient diagnosed with bone-only disease. All remaining patients had extensive abdominal lymph node involvement.

Of the six patients, four received chemotherapy: three receiving cisplatin + etoposide and one receiving carboplatin + docetaxel (Table 1). One patient exhibited partial response, and two demonstrated stable disease. Of four patients, two received second-line chemotherapy, including regimens with irinotecan, gemcitabine, and 5-FU based (FOLFIRI); however, all courses were maintained for one to two cycles with rapid patient deterioration, which precluded further treatment. Of the six patients, three were positively stained for DLL3 (Table 1, Fig. 2). However, only two patients are alive at the time of writing this manuscript (OS: 392 and 1366 days, respectively). Of these patients, one received four courses of chemotherapy (docetaxel + carboplatin), was later switched to ADT, and currently, still displays stable disease response (OS: 1366 days). The second patient refused any upfront chemotherapy and was initiated on ADT alone, resulting in stable disease response.

Notably, the treatment course of the patient who displayed prolonged OS (1366 days, 3.7 years) may be a great reference for future treatment selection. This male patient was 78-year-old upon diagnosis with mixed adenocarcinoma (Gleason 4+3) and neuroendocrine carcinoma. He had no prior diagnosis or treatment for prostate cancer. The initial tumor burden included prostate cancer with rectal and bladder invasion, left hydronephrosis, pelvic lymphadenopathy, and bone metastasis (Fig. 2). The patient underwent TURP pre-chemotherapy initiation. His initial PSA level was 42 ng/mL before initiating chemotherapy, and was then increased to 216 ng/mL post-chemotherapy (four courses of docetaxel + carboplatin). Restaging imaging post-chemotherapy revealed regression of the main tumor and surrounding lymph nodes. Owing to discomfort, the patient was reluctant to receive further chemotherapy. Subsequently, the patient received abiraterone + degarelix as ADT. Consequently, the PSA levels started to decrease, reaching a concentration of 2.5 ng/mL 2-years after the initial diagnosis. Follow-up imaging revealed stable disease response (Fig 2); thus, the patient is alive and, at the time of writing this manuscript, has a good performance status.

3.2. Genomic analysis of NEPC

Herein, three patients underwent multigene panel sequencing of NEC tumor samples. RB1 mutations were found in all three patients, and included *CDH1, ATR, BRCA2, FLCN, RAD51, STK11, KMT2C, ATM, BRCA1, CDKN2C, CHEK1, CHEK2, MRE11A, NF2, TSC1, BARD1, LRP1B, BCL2L1, MLL2*, and *TP53* (Fig. 3). Comparing the mutations found in these three patients with those of the *HRR* mutation genes in the PROPEL study,[21] six genes (*BRCA2, ATM, BRCA1, CHEK1, CHEK2, BARD1*) were found to have overlapped. Five of the six gene mutations (excluding *BRCA2*) were discovered in the same patient. This patient was initially diagnosed with metastatic castration-sensitive prostate cancer (CSPC) (bone metastases) and was started on enzalutamide. Initially, a good PSA response was documented; however, after 1 year of enzalutamide treatment, the disease progressed with the appearance of new bone

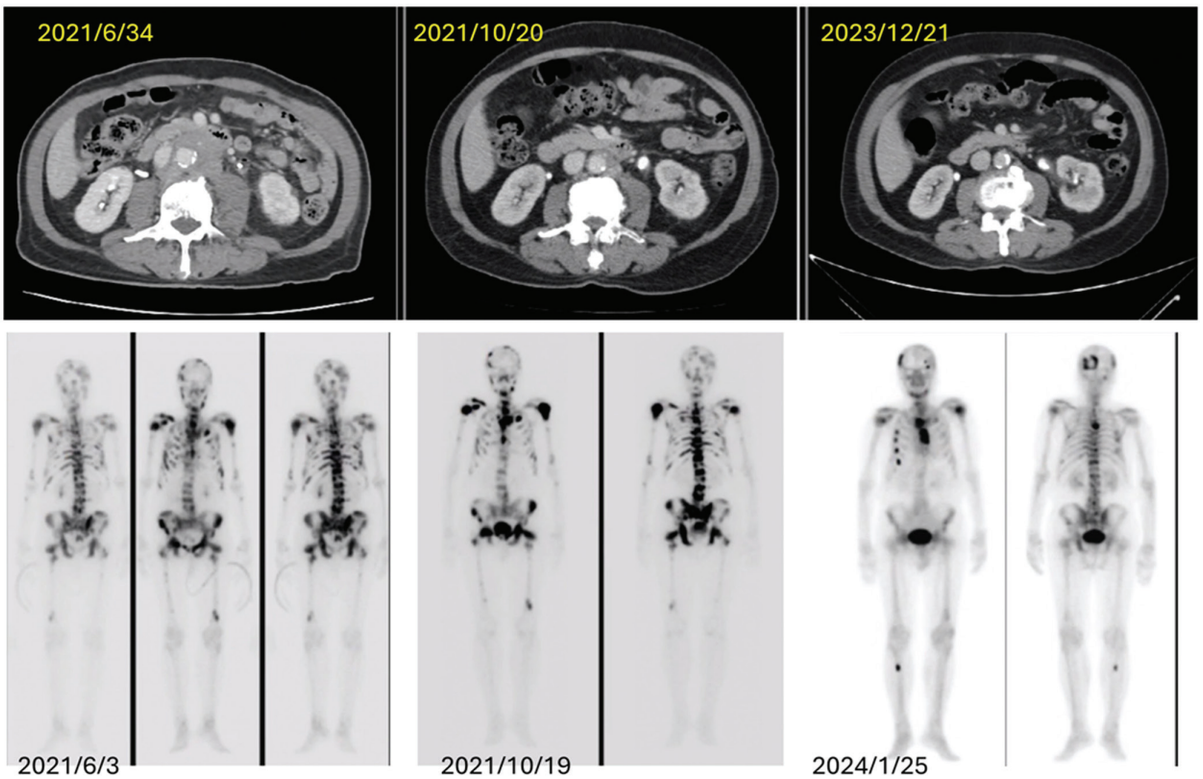

Fig. 2 Serial imaging studies for patient 1. Up, CT studies of abdomen, the image depicts the abdominal lymphadenopathy. Below, Whole-body bone scan images. The respective dates for each captured image taken are recorded. CT = computerized tomographic.

lesions and liver metastases. The PSA level at time of progression was 0.04 ng/mL. Re-biopsy revealed a pathology of pure neuroendocrine carcinoma with no adenocarcinoma components. He received four cycles of cisplatin + etoposide, but the disease rapidly progressed, and expired 5 months post-NEPC diagnoses.

3.3. Literature review of clinical studies on chemotherapy efficacy in prostate neuroendocrine cancer

We retrospectively reviewed the literature on chemotherapy regimens for metastatic NEPC (Section 2 for selection criteria). Of the 961 articles screened, eight studies were included for further analysis,[10,22–28] including 141 patients with metastatic NEPC receiving chemotherapy (Table 2). In all eight studies, the chemotherapy regimen included EP, and the PFS ranged from 3.4 to 10.1 months, OS ranged from 8.4 to 22.4 months, and response rates ranged from 44% to 78%. Generally, these studies were consistent with a dismal OS rate, despite the high response rate to the EP regimen.

4. DISCUSSION

We documented six cases of metastatic NEPC who were treated with chemotherapy, predominantly, an EP-based regimen. Five out of six patients presented with de novo NEPC along with mixed adenocarcinoma and NEPC, in contrast, to the general notion that most NEPC cases are t-NEPC. This may be due to sampling bias; however, many cases may be underdiagnosed due to low re-biopsy rates for advanced prostate cancer. As NHA has been shown to dramatically prolong PFS and OS in metastatic prostate cancer cases, we have speculated that physicians are less inclined to perform re-biopsy during the immediate progression of first-line NHA usage. This may be reflected in our study, that is, the incidence of NEPC was relatively lower (~0.3%) than the reported 15% to 20% in treatment of refractory CRPC.

Herein, all three patients who underwent multigene panel assays had *RB1* mutations. A previous study demonstrated that *RB1* and protein expression loss frequently occur in NEPC.[29] A recent study that genetically profiled 415 NEPC cases, found that 61% of *RB1* were genetically altered[30] and that *RB1* mutant NEPC harbored low PD-L1 expression. Another study performed comprehensive transcriptomic profiling of patients with metastatic CPRC who progressed to NHA, and discovered a 17% incidence of NEPC (t-NEPC).[6] In metastatic CPRC cases, a strong retinoblastoma protein (RB) loss transcriptomic signature was compared to the signature found in adenocarcinoma cases.[6] Therefore, RB expression loss is a strong negative prognostic factor in advanced prostate cancer.[31] Furthermore, *RB1* inactivation is prevalent in small-cell carcinomas of different tumor locations. In SCLC, *RB1* and *TP53* inactivation was observed in nearly all cases in The Cancer Genome Atlas Program (TCGA) cohort study.[32] However, in the context of prostate cancer, it arouses the following question: Does the loss of *RB1* in CRPC drive tumorigenesis toward NEPC? Different mechanisms of NEPC oncogenesis have been proposed.[33] Serial biopsy comparisons between castration-resistant adenocarcinoma and NEPC indicate that the clonal evolution of an AR signaling-resistant phenotype may be a driving force of neuroendocrine development.[34] Oncogene alterations, including *MYC* and extensive methylation changes, which emerged in later clones, suggest that epigenetic dysregulation is a driving force of NEPC.[34]

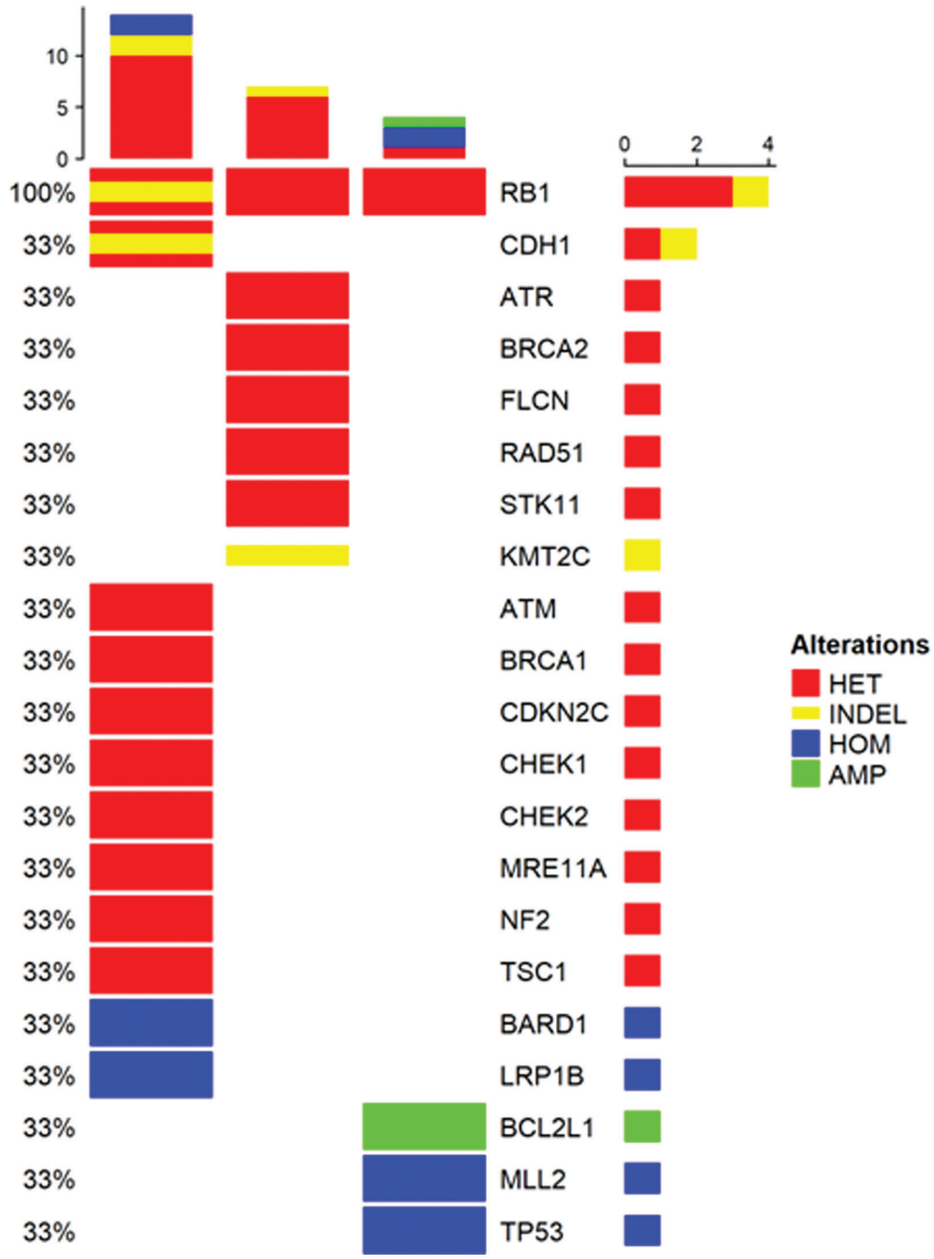

Fig. 3 Oncoprint of the somatic mutations from three patients with NEPC. NEPC = neuroendocrine prostate cancer.

Table 2

Literature review of studies receiving chemotherapy for NEPC

Author(s)	Patients	Regimen	% of 1st line	PFS	OS	ORR	Reference
Baude et al	18	carboplatin/etoposide	83.3	7.9	14.4	58.8	[22]
Amato et al	21	carboplatin/etoposide	100	NA	9.4	62	[23]
Ueki et al	13	EP	100	9.3	22.4	69.2	[24]
Wee et al	7	atezo/carboplatin/etoposide	83.3	3.4	8.4	NA	[25]
Steineck et al	9	EP + estramustine	100	NA	NA	44	[26]
Papandreou et al	36	EP + doxorubicin	100	5..8	10.5	61	[27]
Conteduca et al	21	EP	100	3.8	NA	NA	[10]
Conteduca et al	7	taxane based	100	3.9	NA	NA	[10]
Suzuki et al	9	EP	100	10.1	NA	78	[28]

EP = etoposide + platinum (carboplatin or cisplatin); number of patients = number of patients reported in the study; NA = not available; ORR = objective response rate (%); OS = overall survival (in d); PFS = progression-free survival (in d).

However, this study could not determine a clear-cut, direct progression pathway for NEPC transformation. A recent study reported an *RB1*/*PTEN* conditional double knockout murine model of prostate cancer.[35] Herein, the tumors strongly expressed the neuroendocrine marker, synaptophysin, and an AR-negative phenotype. This study elucidates the possible causative effect of *RB1* loss (accompanied by *PTEN*) as a driving force for neuroendocrine AR signaling, independent of NEPC oncogenesis.

In our study, 50% (3/6) of patients tested positive for DLL3 staining. However, data on DLL3 positivity are limited. Currently, two studies have reported a ~75% positivity rate for DLL3 in NEPC.[20,36] Additionally, the DLL3 targeting antibody-drug conjugate (rovalpituzumab tesirine, Rova-T) showed initial promise in a phase 1 solid tumor basket trial, where one patient with an RB mutation exhibited a good clinical response,[36] which was then discontinued due to failure in a phase 3 SCLC trial. As neuroendocrine carcinomas/small-cell carcinomas have an extremely poor prognosis, the efficacy of DLL3 in targeting bispecific T-cell engagers is promising.[19]

Owing to the rarity of NEPC, only a limited number of case series on chemotherapy outcomes are available in the literature.[22–27] Most studies have consistently reported a high ORR with limited OS. The median OS of approximately 1 year post-first line chemotherapy is starkly different from that of the usual clinical course of metastatic CRPC. Currently, most metastatic small-cell cancers/neuroendocrine cancers at different sites follow the treatment guidelines for SCLC, of which the currently preferred regimens for extensive-stage cancer comprise EP combined with immunotherapy (atezolizumab and durvalumab).[37] Notably, the addition of either atezolizumab or durvalumab to the chemotherapy backbone incrementally increased the patients' OS to <3 months per study. This barely extends the OS by >1 year.[37] Thus, further therapeutic breakthroughs are warranted for better treatment strategies and improved OS values.

In our cohort, only one patient, initially diagnosed with a high lymph node and bone metastasis burden, had prolonged OS lasting >3 years, and his treatment regimen may provide insightful information as a reference. The fluctuations observed in the PSA level in this case suggest that the tumor may have a dominant adenocarcinoma component that responds well to conventional ADT. The initial chemotherapy regimen may have reduced the tumor size and induced immunogenic cell death,[38] leading to prolonged survival. This case raises several hypotheses. Is ADT maintenance following successful chemotherapy-based tumor downsizing a potential treatment approach? Would pure NEPC be distinct from mixed adenocarcinoma and NEPC regarding its sensitivity to androgen deprivation? Finally, similar to the CSPC trials such as PEACE-1[39] and ARASENS,[40] would combining chemotherapy (eg, EP) with ADT be a feasible treatment for mixed adenocarcinoma and NEPC? Based on our results, we suggest the utility of a docetaxel + carboplatin-based regimen as "induction" therapy. This approach may prove efficacious in mixed prostate adenocarcinoma/NEPC and warrants further investigation.

This study has many limitations. First, this study is severely limited by its small sample size. However, we have detailed the treatment landscape and included a mini-literature review that summarized the current data in the existing literature regarding t-NEPC. Therefore, our study is considered a mini-review of real-world cases and detailed discussion of specific cases. Notably, in the real-world, DLL3 expression is comparable to the reported (also limited) cases in the literature. Considering the current success and huge potential of DLL3 targeting agents in other cancers,[19] our study reveals a potential therapeutic development opportunity for t-NEPC.

In conclusion, we documented a cohort of six NEPC cases treated with chemotherapy, coupled with genomic features analysis, and compared it with the relevant cases in the literature. Owing to the limited number of relevant cases, this study added valuable insight to the literature in regard to the clinical management of NEPC. In the future, further translational studies and larger clinical trials are warranted in this patient population for more in-depth comprehension of NEPC management and treatment.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A307.

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