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Review

Second-Line Systemic Therapy for Highly Aggressive Neuroendocrine Prostate Cancer

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Abstract. *Neuroendocrine prostate cancer (NEPC) is generally an aggressive form of prostate cancer that can arise de novo or develop as a castration-resistant mechanism. While first-line platinum-based chemotherapy is effective against NEPC, its limited response duration and subsequent treatments pose significant clinical challenges. Standard second-line treatments have not been established due to the limited data available. The aim of this review was to reveal the current status of second-line therapy for NEPC. A literature search was conducted using PubMed and Web of Science and a total of 13 articles were included in this review. Prospective and retrospective studies demonstrated that treatment outcome of second-line therapy using platinum with etoposide or docetaxel was unfavorable and progression-free survival was 3 months or shorter. Amrubicin and irinotecan were also frequently used as second-line therapy, however, efficacy of these agents was modest and response duration was less than 6 months. NEPC patients with homologous recombination repair gene alterations may benefit from treatment with poly (ADP-ribose) polymerase (PARP) inhibitors. Ongoing clinical studies investigate various agents, including immune checkpoint inhibitors, molecularly targeted agents, and PARP inhibitors. With the increasing recognition and active biopsy of NEPC lesions, the number of NEPC patients is anticipated to rise. Accumulating more knowledge and experience is crucial in developing novel treatment strategies to combat this disease.*

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Neuroendocrine prostate cancer (NEPC) is often a highly aggressive form characterized by treatment resistance and poor prognosis (1, 2). NEPC is typically treated with cisplatin-based chemotherapy as a standard first-line therapy. However, clinical data on second-line therapy are limited because of its low incidence and the lack of standard therapies. Developing effective second-line and beyond treatments for this highly aggressive cancer is a major clinical challenge. We aimed to review and summarize the oncological outcomes of NEPC patients undergoing second-line systemic therapy. The data used in this article were obtained from PubMed, Web of Science, and Clinical Trials gov.

Overview and Clinical Features of NEPC

NEPC arises *de novo* or develops during androgen deprivation therapy (ADT) as one of the castration-resistant mechanisms (treatment-related neuroendocrine prostate cancer; t-NEPC) (2, 3).

De novo NEPC is rare and its incidence has been reported to be <2% of prostate cancer (4). T-NEPC is commonly detected and up to 30% of metastatic CRPC cases have immuno-histochemical features of neuroendocrine differentiation (5-8).

Pathologic classification. The Prostate Cancer Foundation proposed a pathologic classification of NEPC in 2013 as follows: 1) Usual prostate adenocarcinoma with NE differentiation; 2) Adenocarcinoma with Paneth cell-like neuroendocrine differentiation; 3) Carcinoid tumor; 4) Small cell neuroendocrine carcinoma; 5) Large cell neuroendocrine carcinoma; and 6) Mixed neuroendocrine carcinoma-acinar adenocarcinoma. In this classification, t-NEPC was classified

in an independent category, castration-resistant prostate cancer (CRPC) with small cell carcinoma (SCC) -like clinical presentation (9). The World Health Organization (WHO) proposed a similar classification in 2016 (10). More recently, "treatment-related neuroendocrine prostatic carcinoma" was included, as an independent category without the need to distinguishing, for example, between small cell and large cell neuroendocrine carcinoma, in the 2022 WHO classification for cases demonstrating complete or partial neuroendocrine differentiation after ADT (11).

NEPC and hormone resistance. Several studies have demonstrated that ADT, as well as the chemotherapeutic agent docetaxel, could induce neuroendocrine differentiation in prostate cancer cells (12, 13). Novel androgen receptor axis targeted agents (ARATs) such as abiraterone, enzalutamide, apalutamide, and darolutamide strongly suppress androgen receptor activity and prolong the survival of patients with CRPC. Recently, ARATs and docetaxel are also used as first-line therapy for hormone-sensitive prostate cancer (14). The number of patients with NEPC appears to be increasing due to the following reasons: 1) long-term exposure of prostate cancer cells to ADT, ARATs, and/or docetaxel; 2) recognition of this variant; and 3) active biopsy of CRPC lesions. Therefore, the diagnosis and treatment of NEPC are becoming a very important clinical issue.

Clinical features. The clinical features of NEPC include low serum prostate-specific antigen, frequent visceral and bulky soft-tissue metastases (≥5 cm), bulky (≥5 cm) high-grade (Gleason score ≥8) prostate nodule(s), rapid progression, and limited duration (≤6 months) of response to ADT (15).

Pure NEPC is associated with a worse prognosis than mixed NEPC. There was no significant difference in overall survival (OS) from the time of NEPC diagnosis between *de novo* NEPC and t-NEPC (1). Patients with NEPC typically undergo chemotherapy with regimens used for small cell lung cancer (SCLC) because of their pathological and biological similarity (15, 16). NEPC was initially sensitive to platinum-based chemotherapy, such as a combination of platinum plus etoposide or docetaxel, with an objective response rate of 40%-67% (2, 17-19). However, the disease inevitably progresses with a short duration of response, and median progression-free survival (PFS) and OS were 2-8 months and 8-19 months, respectively (2, 16, 19).

Second-line Systemic Therapy for NEPC

The disease rapidly progresses after a short-term response to first-line therapy. Only 37% of patients received second-line systemic therapy, and the time from first-line to second-line therapy was 8 months in metastatic NEPC in the real world (20). Effective second-line and beyond therapies are mandatory to improve the survival of patients with NEPC. Standard second-line therapy has yet to be established, and various second-line regimens have been reported.

A few studies have reported second-line treatments for extra-pulmonary neuroendocrine carcinoma, including genitourinary origin (21, 22). As second-line therapy, FORFIRI (5-fluorouracil, leucovorin, irinotecan), FOLFOX (oxaliplatin, leucovorin, 5-fluorouracil), and CATEM (capecitabine, temozolomide) have been used for gastroenteropancreatic neuroendocrine cancer, showing objective response rates [complete response (CR) + partial response (PR)] of around 30% and median PFS of 4-6 months (22). McNamara *et al*. (21) reviewed 19 studies, involving 582 patients who had received second-line treatment for extra-pulmonary neuroendocrine carcinoma. The objective response rate to the second-line therapies were 0%-50%, While PFS and OS after second-line therapies were 1-6 months and 3-22 months, respectively.

To obtain the clinical data on second-line systemic treatments for NEPC, a literature search was conducted using PubMed and Web of Science. Studies were included if they: 1) were written in English; 2) were clinical studies (case reports, retrospective and prospective studies); or 3) reported data on the treatments and outcomes for NEPC. The exclusion criteria were: 1) non-English literature; 2) insufficient clinical data; and 3) meta-analyses, literature reviews, systematic reviews, editorials, letters, or book chapters.

Thirteen articles (9 case reports, 3 retrospective studies, 1 prospective study) met the inclusion criteria. One hundred and thirty-nine patients from the literature, in addition to four of our unpublished cases, who received second-line systemic treatment for NEPC were thus used in this review.

Table I summarizes second-line systemic treatments used for NEPC. Amrubicin (AMR), irinotecan, platinum, etoposide, and docetaxel, either alone or in combination of two or three, were frequently used as second-line chemotherapy.

AMR. AMR is an inhibitor of DNA topoisomerase II. A phase II trial demonstrated that AMR exerted significant activity against refractory or relapsed SCLC after platinum-based chemotherapy (23-34).

In a total of 12 NEPC patients, including 2 cases reported by our group, who had been treated with AMR were identified in the literature (23-28). First-line therapies for these patients were etoposide plus platinum (N=10) and cisplatin plus irinotecan (N=2). An objective response to AMR was evaluated in 10 patients. PR and stable disease (SD) were achieved in 6 (60%) and 3 (30%) patients, respectively, whereas progressive disease (PD) was noted in only one patient. PFS was shorter than 6 months in most cases, except one with a PFS of 17 months (28). AMR was thus active in some patients; however, the duration of response was very limited.

Table I. *First-line and second-line treatments for neuroendocrine prostate cancer.*

Authors, Year (Ref)	No. of patients	*De novo* or t-NEPC	1st-line chemotherapy				Metastatic lesion	2nd-line chemotherapy					
			Agent	No. of cycle	Response	PFS (M)		Agent	No. of cycle	Radiation	Response	PFS (M)	OS (M)
Our case	1	*De novo*	EP	5	PR	6.5	Liver, bone, LN	AMR	4	No	PR	4	7
Suzuki *et al*., 2020 (23)	1	t-NEPC	EP	6	PR	x	LN	AMR	6	No	PR	6	x
Ozawa *et al*., 2020 (24)	1	t-NEPC	CBDCA+ETP	4	x	3	Liver	AMR	8	No	PR	x	12+
Kobayashi *et al*., 2020 (25)	1	t-NEPC	CDDP+CPT11	6	PR		Brain, LN	AMR	7	No	PR	x	6
Suzuki *et al*., 2020 (23)	1	t-NEPC	EP	5	PR	x	LN, bone, lung, liver	AMR	8	No	x	6	x
Ueki *et al*., 2023 (26)	1	x	EP	6	PR	x	x	AMR	6	x	PR	x	x
Ueki *et al*., 2023 (26)	1	t-NEPC	EP	2	PD	x	x	AMR	9	x	PR	x	x
Ueki *et al*., 2023 (26)	1	t-NEPC	EP	10	PR	x	x	AMR	2	x	SD	x	x
Ueki *et al*., 2023 (26)	1	t-NEPC	EP	6	CR	x	x	AMR	3	x	SD	x	x
Maesaka *et al*., 2019 (27)	1	*De novo*	CDDP+CPT11	2	PD	x	Bone	AMR	15	Yes	SD	x	x
Our case	1	t-NEPC	EP	3	PR	4	Liver, LN	AMR	1	Yes	PD	2	4
Hirai *et al*., 2015 (28)	1	t-NEPC	CBDCA+ETP	12	CR	x	LN	AMR	12	Yes	x	17	18
Yamada *et al*., 2009 (29)	1	*De novo*	EP	4	x	x	Bone, liver, LN, meninges, brain	CBDCA+CPT11	4	No	x	x	x
Iwamoto *et al*., 2022 (19)	1	*De novo*	EP	4	PR	6.1	x	CBDCA+CPT11	4	Yes	PR	4.21	x
Iwamoto *et al*., 2022 (19)	1	*De novo*	EP	3	PR	7.3	x	CBDCA+CPT11	7	Yes	PR	6.7	x
Our case	1	t-NEPC	EP	4	PR	5	LN	CDDP+CPT11	1	No	PD	1	7
Our case	1	*De novo*	EP	6	CR	9	Bone, lung	CDDP+CPT11	4	No	PR	6.5	24
Iwamoto *et al*., 2022 (19)	1	t-NEPC	CBDCA+DTX	3	PR	27.5	x	CDDP+CPT11	2	Yes	SD	3.88	x
Iwamoto *et al*., 2022 (19)	1	t-NEPC	EP	3	PR	3	x	CPT11	2	No	PD	0.53	x
Iwamoto *et al*., 2022 (19)	1	t-NEPC	CBDCA+ETP	3	SD	8.3	x	CPT11	2	Yes	PD	1.45	x
Iwamoto *et al*., 2022 (19)	1	t-NEPC	CBDCA+ETP	5	PD	1.6	x	CPT11	5	Yes	PD	1.64	x
Iwamoto *et al*., 2022 (19)	1	t-NEPC	DTX	6	PD	1.8	x	CDDP+ETP	3	No	SD	4.63	x
Katou *et al*., 2008 (30)	1	*De novo*	AMR	1	PR	x	LN, bone	CBDCA+ETP	2	Yes	PD	x	5
Miyazawa *et al*., 2021 (31)	1	t-NEPC	EP	12	x	15M	LN, bone, Liver	Olaparib	po	No	PR	x	x
Miyazawa *et al*., 2021 (31)	1	t-NEPC	CBDCA+ETP	17		x	LN	Olaparib	po	No	PR	x	x
Aparicio *et al*., 2013 (32)	74	Both	CBDCA+DTX	4 (median)	x	5.1 (median)	x	CDDP+ETP	4 (median)	x	x	3.0 (median)	x
Conteduca *et al*., 2019 (1)	19	t-NEPC	Platinum, Taxane, ETP	x	x	x	x	Platinum, taxane, EP	x	x	x	x	x
Conteduca *et al*., 2019 (1)	9	*De novo*	Platinum, Taxane, ETP	x	x	4.9	x	Platinum, EP, DTX	x	x	x	2.3	2.5
Yildirim *et al*., 2008 (33)	1	*De novo*	EP	6	PR	x	LN	VCR, ADM, CPA	2	No	PD	x	x
Iwamoto *et al*., 2022 (19)	1	t-NEPC	DTX	5	SD	2.7	x	CBZ	12	Yes	SD	9.53	x
Iwamoto *et al*., 2022 (19)	1	De novo	CBDCA+ETP	7	SD	20.7	x	Everolimus	2	Yes	PD	0.79	x

ADM: Adriamycin; AMR: amrubicin; CBZ: cabazitaxel; CBDCA: carboplatin; CDDP: cisplatin; CPT11: irinotecan; CPA: cyclophosphamide; CR: complete response; DTX: docetaxel; EP: etoposide plus cisplatin; ETP: etoposide; LN: lymph node; OS: overall survival from second-line therapy; PD: progressive disease; PFS: progression-free survival; po: per os; PR: partial response; SD: stable disease; t-NEPC: treatment-related neuroendocrine prostate cancer; VCR: vincristine; x: not reported.

Table II. *Ongoing clinical trials for neuroendocrine prostate cancer.*

NCT number	Phase	Agent	Primary outcome measure
NCT03551782	I	Cetrelimab, Apalutamide	Adverse events, PSA response
NCT04926181	II	Apalutamide + Cetrelimab	Composite response rate*
NCT03582475	I	Pembrolizumab + CBDCA or CDDP or DTX or Etoposide	DRR, ORR, DOR, PFS, rPFS, OS, PSA response
NCT03333616	II	Ipilimumab + Nivolumab	Objective response rate
NCT02834013	II	Nivolumab + Ipilimumab	ORR
NCT03866382	II	Ipilimumab + Nivolumab + Cabozantinib	ORR
NCT05582031	II	Regorafenib + Tislelizumab	PFS
NCT03179410	II	Avelumab	ORR
NCT03910660	I	BXCL701 + Pembrolizumab	CR rate, Objective response
	II	BXCL701	
NCT05652686	I	PT217	DLT, MTD recommended Phase II dose
NCT04754425	II	Erdafitinib	BAP modulation
NCT04592237	II	CBZ, CBDCA, Cetrelimab, Niraparib	PFS
NCT03263650	II	CBZ + CBDCA Olaparib	PFS
NCT03696186	II	DTX + CBDCA DTX	OS
NCT05691465	II	Lutetium Lu 177	Objective response rate

BAP: Bone specific alkaline phosphatase; CBDCA: carboplatin; CBZ: cabazitaxel; CDDP: cisplatin; CR: complete response; DLT: dose limiting toxicity; DOR: duration of response; DRR: durable response rate; DTX: docetaxel; MTD: maximum tolerated dose; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; rPFS: radiographic PFS; PSA: prostate-specific antigen; *PSA decline and objective response.

Inirotecan. Irinotecan is a prodrug targeting topoisomerase I and is frequently used for SCLC in combination with cisplatin (35). Irinotecan, with or without cisplatin, inhibited the growth of patient-derived prostatic SCC xenografts in a mouse model (36).

We identified 9 cases who had received irinotecan alone or combined with cisplatin or carboplatin as second-line therapy (19, 29). When combined with cisplatin or carboplatin, PR was achieved in 3 of 5 evaluable patients with a median PFS of 4.2 (range=1-6.7) months. All 3 patients receiving irinotecan alone showed PD. Combined therapy with cisplatin or carboplatin had moderate activity, but irinotecan monotherapy was inactive as a second-line treatment.

Platinum, etoposide, docetaxel. Cisplatin or carboplatin plus etoposide is a standard systemic therapy for SCLC (35) and is also frequently used for NEPC as first-line therapy. Aparicio *et al*. (32) conducted a phase II trial of second-line EP (120 mg/m^2 etoposide plus 25 mg/m^2 cisplatin administrated daily for 3 days every 3 weeks) following first-line carboplatin and docetaxel in 120 patients with t-NEPC. Of 105 patients, 74 (70.5%) received second-line EP after progression on first-line therapy. The median cycle of EP was 4 (range=1-6). Seventy-two (97.3%) of 74 patients experienced disease progression with a median PFS of 3 months after receiving EP. The median OS was 16 months after first-line therapy.

In a case report where EP was used as second-line after first-line docetaxel, the objective response was SD, and PFS was 4.6 months (19). In another case using etoposide plus carboplatin after first-line AMR, the objective response was PD, and OS after initiation of second-line therapy was only 5 months (30).

Conteduca *et al*. (1) reviewed treatment and outcome data in 87 patients with NEPC. Forty-seven (54%) and 40 (46%) patients presented *de novo* NEPC and t-NEPC, respectively. Thirty-one (66%) *de novo* patients received chemotherapy. The most common first-line chemotherapy regimens were platinum plus taxane or etoposide (N=25) followed by docetaxel (N=3). Nine patients received second-line chemotherapy with platinum alone (N=1), platinum plus etoposide (N=4), or docetaxel (N=4). Median PFS on second-line therapy was only 2.33 months overall and 2.52 months for platinum alone. Among the 40 patients with t-NEPC, 19 received second-line chemotherapy (platinum doublet, N=15, docetaxel, N=4). The median PFS after NEPC diagnosis was 4.8 months. Taken together, the response duration to second-line regimens, using platinum, etoposide, and docetaxel, was extremely short.

PARP inhibitors. PARP inhibitors are effective for various cancers with homologous recombination repair (HRR) gene alterations. Olaparib, a PARP inhibitor, is effective for patients with metastatic CRPC harboring BRCA gene alterations (37). Miyazawa *et al*. (31) reported 2 cases with BRCA2 alteration who had received olaparib as second-line treatment for NEPC. Olaparib was effective, and PR was achieved in these 2 cases. Another report also demonstrated the efficacy of first-line olaparib in a patient with NEPC harboring the BRCA1 alteration (38). The frequency of HRR gene alterations in NEPC was similar to that in CRPC exhibiting conventional

adenocarcinoma with no neuroendocrine differentiation (1), and PARP inhibitors are a valuable option for treating NEPC harboring HRR gene alterations.

Ongoing clinical trials and future direction. Table II lists the ongoing clinical trials for NEPC (39). In these trials, immune checkpoint inhibitors, molecularly targeted agents, PARP inhibitors, platinum-based agents, taxanes, and radiopharma-ceutical agents are being investigated. These studies may provide effective future treatment strategies for NEPC.

A better understanding of the biology of NEPC is mandatory for developing effective treatments. Beltran *et al*. (40) found frequent overexpression and gene amplification of Aurora kinase A (AURKA), along with MYCN amplification in NEPC cells. AURKA and MYCN cooperatively induced neuroendocrine phenotype in human prostate cancer cells and an Aurora kinase inhibitor, PHA-739358 (danusertib), inhibited the tumor growth in mouse NEPC models. However, a phase II clinical trial failed to demonstrate the efficacy of danusertib for CRPC (41). Promising therapeutic molecular targets have not been identified yet. Further studies are required to identify the principal drivers of NEPC and ultimately develop therapeutic strategies.

Conclusion

NEPC is a highly aggressive form of prostate cancer with a poor prognosis. The number of NEPC patients is increasing and the development of effective treatments for NEPC remains an important clinical challenge. NEPC is often sensitive to first-line platinum-based chemotherapy with a limited duration of response. Second-line treatment options and their efficacy are even very limited. Dramatic improvement may thus not be anticipated by currently available chemotherapeutic agents. Accordingly, it is critical to determine underlying mechanisms of disease progression and treatment resistance for the identification of promising therapeutic targets. Novel therapeutic approaches using molecularly targeted and immuno-oncology agents may lead to considerable improvement in outcomes of patients with NEPC.

Conflicts of Interest

The Authors declare that there are no conflicts of interest.

Authors' Contributions

N.F.: Conceptualization and design, writing—original draft preparation; Y.N., A.M., I.T.: Acquisition of data and the analysis; K.H.: Review and editing; H.M.: Supervision, review, and revision of the manuscript. All Authors read and approved the final version of the manuscript.

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