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Review

The Revival of Estramustine- Re-evaluating an Antimicrotubular Agent in Castration-Resistant Prostate Cancers

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Abstract

Estramustine phosphate (EMP), a nitrogen mustard derivative of estradiol synthesized in the 1960s, was initially developed for hormone-related malignancies but later found clinical application in prostate cancer. Although early use demonstrated modest response rates without survival benefit, subsequent investigations revealed a unique antimicrotubular mechanism distinct from classical alkylating agents. This discovery renewed interest in estramustine as part of combination chemotherapy, particularly with taxanes such as docetaxel and paclitaxel. Clinical studies have demonstrated improved prostate-specific antigen (PSA) responses and progression outcomes when estramustine is combined with taxanes. However, its use is limited by increased risks of thromboembolic and cardiovascular complications. In the contemporary era of advanced therapies for castration-resistant prostate cancer (CRPC), including androgen receptor pathway inhibitors and targeted treatments, the role of estramustine remains a subject of active discussion. This review evaluates the pharmacological properties, preclinical rationale, clinical evidence, and current relevance of estramustine in CRPC management, with particular emphasis on combination strategies and risk–benefit considerations.

Keywords: Castration-resistant prostate cancer, estramustine, docetaxel, chemotherapy, PSA response, combination therapy

Introduction

Estramustine phosphate (EMP), a nitrogen mustard derivative of estradiol, was originally synthesized in the 1960s with the aim of developing a targeted therapy for breast cancer [1]. This initial indication was abandoned following unfavourable clinical trial outcomes; however, subsequent administration in a patient with advanced castration-resistant prostate cancer (CRPC) and severe metastatic pain resulted in a notable clinical response [2]. This observation redirected clinical development toward prostate cancer, and within a few years, EMP became a widely used treatment in regions including Scandinavia, Germany, and Japan [3-5].

In 1981, the U.S. Food and Drug Administration approved estramustine for the management of metastatic castration-resistant prostate cancer (mCRPC) [6]. Early clinical studies demonstrated objective response rates of approximately 20–30%, with more than half of patients experiencing symptomatic improvement and a prostate-specific antigen (PSA) decline exceeding 50% [5,7–11]. However, these responses were not associated with a significant prolongation of progression-free survival or overall survival [11].

With the emergence of more effective chemotherapeutic strategies, particularly the introduction of mitoxantrone plus prednisone as standard care in the United States, the clinical use of estramustine declined [11]. Nevertheless, preclinical interest persisted. Studies in the 1980s established that estramustine exerts its antitumor effects primarily through antimicrotubular and antimitotic mechanisms, rather than through DNA alkylation [14–18].

These mechanistic insights provided a rationale for combination strategies with other microtubule-targeting agents, including vinca alkaloids and taxanes [18–21]. Consequently, estramustine has been investigated in combination with docetaxel, a cornerstone therapy for mCRPC [28–31]. Clinical studies suggest

that this combination improves biochemical response rates and progression-related outcomes compared with docetaxel alone, although the magnitude of survival benefit remains modest and must be balanced against increased toxicity [31–33].

This review summarizes the pharmacological basis, clinical evidence, and evolving role of estramustine as an antimicrotubular agent within the contemporary management of mCRPC.

Preclinical Findings

Mechanism of action

Estramustine was originally designed with the hypothesis that the estradiol moiety would serve as a carrier to deliver a nitrogen mustard component selectively to estrogen receptor–expressing cells. Within these cells, the inactive mustard moiety was expected to be enzymatically cleaved and activated, thereby exerting an alkylating cytotoxic effect. However, this proposed mechanism was not supported by subsequent experimental findings.

Preclinical investigations demonstrated that estramustine does not exert cytotoxicity through DNA alkylation. Instead, the compound exhibited significant antitumor activity across a variety of experimental systems. Estramustine inhibited the growth of estrogen-resistant DMBA-induced mammary tumors in vivo [12], and reduced cell proliferation and clonogenic survival in multiple in vitro models, including DU145 human prostate carcinoma cells [13], HeLa and Walker 256 carcinoma cells [14], and DU145 and PC-3 prostate cancer cell lines [15]. These findings were further supported by in vivo studies, where estramustine demonstrated cytotoxic effects in DU145 xenografts implanted in nude mice [16].

Further mechanistic studies revealed that estramustine-induced cytotoxicity is not associated with DNA strand breaks or cross-link formation [14,17]. Instead, treatment leads to a marked increase in the mitotic index due to arrest of cells in metaphase [15-17]. The arrested cells exhibit features characteristic of stathmokinetic agents such as colchicine and vinca alkaloids, indicating disruption of mitotic progression.

Subsequent research has established that estramustine exerts its antimitotic effects through interactions with microtubular structures. Specifically, estramustine binds to tubulin [18] and microtubule-associated proteins [19-23], leading to depolymerization of cytoplasmic microtubules [18-20,24] and inhibition of microtubule assembly [19,21-23]. Additionally, estramustine disrupts the nuclear matrix [25]. Given the critical role of microtubules in mitotic spindle formation and intracellular transport, their disruption ultimately results in cell death. These findings indicate that interference with microtubule dynamics represents the primary cytotoxic mechanism of estramustine.

Synergy with taxanes

The antimicrotubular mechanism of estramustine provides a strong rationale for combination with taxanes, which exert their cytotoxic effects by stabilizing microtubules and preventing their depolymerization. This complementary interaction may enhance disruption of microtubule dynamics, resulting in increased mitotic arrest and inhibition of tumor cell proliferation.

Preclinical studies support this hypothesis. Synergistic activity between estramustine and paclitaxel has been demonstrated in DU145 prostate cancer cells, where combination treatment produced greater-than-additive inhibition of cell survival in both wild-type and estramustine-resistant cell lines [26].

The combination of estramustine and docetaxel has also been evaluated in multiple preclinical models. In vitro studies using PC-3 and Dunning R-3327 prostate carcinoma cell lines showed heterogeneous effects: estramustine did not significantly alter docetaxel sensitivity in PC-3 cells, whereas it enhanced docetaxel activity in R-3327 cells [27]. In vivo, the combination resulted in significantly greater tumor reduction compared with either agent alone, suggesting improved efficacy, potentially at lower doses.

Additional in vivo studies using PAC120 xenograft models demonstrated that estramustine alone had limited antitumor activity but potentiated the effect of docetaxel in hormone-independent sublines [28]. Similarly, Dahmani et al. reported a significant prolongation of tumor growth delay (18 to 50 days, $p < 0.05$) with the combination in docetaxel-resistant models. However, these findings are not entirely consistent; Fizazi et al. reported no significant enhancement of docetaxel activity with the addition of estramustine in several preclinical models of advanced prostate cancer [29].

Overall, these data provide supportive-though not uniformly consistent-preclinical evidence for the potential benefit of combining estramustine with taxanes, thereby forming the basis for subsequent clinical investigation in castration-resistant prostate cancer.

Clinical investigations of estramustine combined with paclitaxel

Estramustine in combination with paclitaxel has been evaluated in several phase II studies in patients with castration-resistant prostate cancer (CRPC) (Table 1). In an early trial, paclitaxel (120–140 mg/m²) was administered as a continuous infusion over three days every three weeks, in combination with daily estramustine at 600 mg/m² [30]. A prostate-specific antigen (PSA) response (≥50% decline) was observed in 65% of 23 evaluable patients, indicating substantial antitumor activity. In a subsequent study using a similar regimen, a PSA response was reported in 53% of 32 evaluable patients, including one complete response in a patient with measurable disease [31]. These findings supported the rationale for combining agents targeting microtubule dynamics through complementary mechanisms.

Later studies predominantly employed weekly paclitaxel schedules (60–150 mg/m²), combined with estramustine doses ranging from 420 to 980 mg administered on the day of paclitaxel infusion as well as on the preceding and following days. Across these studies, PSA response rates ranged from 42% to 67% [32–35]. Overall, the combination was considered active and generally well tolerated in this patient population [35].

A randomized phase II trial further evaluated the addition of estramustine to weekly paclitaxel in 163 patients [36]. Paclitaxel (100 mg/m²) was administered weekly for three consecutive weeks in a four-week cycle, with estramustine (840 mg) given around each infusion. The PSA response rate was significantly higher in the combination arm compared with paclitaxel alone (47% vs 27%, $p < 0.01$). Median overall survival was also mod-

Table 1. Summary of Phase II trials evaluating estramustine in combination with paclitaxel in CRPC

Study (Ref)	Patients (n)	Paclitaxel Regimen	Estramustine Regimen	PSA Response ≥50%	Key Findings
Hudes et al. [30]	23	120–140 mg/m² (3-day infusion, q3w)	600 mg/m² daily	65%	High activity; early signal of efficacy
Hudes et al. [31]	32	Same as above	Same as above	53%	Confirmed activity; 1 CR reported
Weekly trials [32–35]	30–60	60–150 mg/m² weekly	420–980 mg around infusion	42–67%	Active and generally well tolerated
Kuruma et al. [34]	Small cohort	100 mg weekly	280 mg BID	67%	Good response; manageable toxicity
Vaughn et al. [35]	Multicenter	Weekly regimen	Combined schedule	~60%	Consistent activity across centers

Table 2. Summary of clinical trials evaluating estramustine in combination with docetaxel in CRPC

Study (Ref)	Study Type	Patients (n)	Regimen	PSA Response ≥50%	Survival / Outcome	Key Findings
Savarese et al. [40,41]	Phase II	39	Docetaxel 70 mg/m² q3w + EMP	69%	OS ~20 months	Effective, tolerable
Sinibaldi et al. [43]	Phase II	—	Single-day EMP + docetaxel	45%	OS 13.5 months	Lower toxicity, reduced efficacy
Nelius et al. [45]	Phase II	72	3-day vs 5-day EMP	~70%	Similar outcomes	No major schedule difference
Copur et al. [46,47]	Phase II	—	Weekly docetaxel + EMP	~70%	—	High activity
Oudard et al. [48]	Randomized Phase II	130	Docetaxel + EMP vs mitoxantrone	63–67% vs 18%	OS 18 vs 13 months	Superior to mitoxantrone
Petrylak et al. [51]	Phase III	674	Docetaxel + EMP vs mitoxantrone	50% vs 27%	OS 17.5 vs 15.6 mo	Modest survival benefit, ↑ toxicity
Eymard et al. [55]	Phase II	92	Docetaxel ± EMP	68% vs 30%	OS 19.3 vs 17.8 mo	Improved response with EMP

estly improved (16.1 vs 13.1 months, p = 0.049). These results suggest a potential clinical benefit of the combination, although the magnitude of survival advantage remains limited.

Efforts to enhance treatment efficacy have included the addition of other cytotoxic agents. Combinations of estramustine and paclitaxel with etoposide and/or carboplatin have been investigated in multiple phase II trials [37–39]. These regimens generally achieved PSA response rates of approximately 60%, comparable to those observed with the estramustine–paclitaxel doublet alone. In smaller studies, alternative dosing schedules have also shown promising activity; for example, weekly paclitaxel (100 mg) combined with estramustine (280 mg twice daily) resulted in PSA declines ≥50% in up to 67% of patients, with manageable toxicity.

More intensive regimens incorporating carboplatin have also been explored. Studies by Segawa et al. and Yasafuka et al. reported enhanced antitumor activity with estramustine–paclitaxel-carboplatin combinations in progressive CRPC, albeit with increased toxicity that remained within acceptable limits. Overall, these findings indicate that estramustine combined with paclitaxel demonstrates consistent antitumor activity in CRPC. However, the incremental benefit of adding further cytotoxic agents appears limited, and treatment intensification must be balanced against the risk of increased toxicity.

Clinical investigations of estramustine combined with docetaxel

Phase II studies

Docetaxel in combination with estramustine has been evaluated in multiple phase II studies in patients with castration-resistant prostate cancer (CRPC) (Table 2). In an early trial, docetaxel (70 mg/m²) was administered as a one-hour infusion every three weeks, in combination with estramustine (10 mg/kg/day in divided doses) given on the day of docetaxel infusion, as well as one day prior and three days following treatment [40]. Low-dose hydrocortisone was also administered. A prostate-specific antigen (PSA) response (≥50% decline) was observed in 69% of 39 evaluable patients. The regimen was considered effective and reasonably well tolerated, supporting further investigation in phase III trials [41]. Median overall survival was reported to be approximately 20 months, and quality-of-life analyses indicated improvement in prostate cancer–related symptoms despite treatment-related adverse effects [42].

To reduce toxicity associated with prolonged estramustine exposure, alternative dosing strategies have been explored. In one phase II study, estramustine was administered as a single-day regimen (280 mg every 6 hours for five doses) in combination with docetaxel [43]. This approach resulted in a lower PSA response

rate (45%) and shorter median overall survival (13.5 months), although toxicity-articularly thromboembolic events and gastrointestinal symptoms-was reduced. Notably, outcomes appeared inferior compared with multi-day estramustine schedules [41,44].

Subsequent randomized phase II studies have investigated variations in dosing schedules. A study including 72 patients demonstrated no significant difference in efficacy between low-dose estramustine administered over three days and higher-dose regimens over five days [45]. Additional studies have reported PSA response rates of approximately 70% with three-day estramustine schedules combined with weekly docetaxel [46,47].

The optimal dosing schedule was further evaluated in a randomized phase II trial involving 130 patients [48]. Patients were assigned to one of three treatment arms: (A) docetaxel (70 mg/m², day 2) with estramustine (280 mg three times daily on days 1–5 and 8–12); (B) docetaxel (35 mg/m², days 2 and 9) with the same estramustine schedule; or (C) mitoxantrone (12 mg/m², day 1). All patients received daily prednisone. PSA response rates were 67% and 63% in arms A and B, respectively, compared with 18% in the mitoxantrone arm. Median survival was longer in the estramustine–docetaxel groups (18 months vs 13 months), and time to PSA progression was significantly prolonged. No substantial difference in efficacy was observed between weekly and three-weekly docetaxel regimens.

Combination Strategies with Additional Agents

Various agents have been combined with estramustine–docetaxel in an effort to improve therapeutic outcomes, including carboplatin, etoposide, zoledronic acid, celecoxib, calcitriol, suramin, trastuzumab, bevacizumab, vinorelbine, and cyclophosphamide .

The addition of suramin to estramustine–docetaxel demonstrated high activity in a small cohort (n=42), with reported PSA response rates approaching 100% and median overall survival of 132 weeks [49]. However, these findings require confirmation in larger studies.

Combination regimens including bevacizumab have also shown encouraging activity, with PSA declines ≥50% observed in approximately 75% of patients and median overall survival of around 24 months. However, these regimens were associated with increased toxicity, including neutropenia, fatigue, and thromboembolic events. The addition of etoposide has demonstrated variable efficacy, with response rates ranging from approximately 59% to 78%, depending on dosing schedules. Higher-dose regimens appeared more active but were associated with increased toxicity.

Other combinations, including vinorelbine and vinblastine, have yielded mixed or limited benefits. While some studies reported modest improvements in progression-related outcomes, overall survival benefits were inconsistent. Similarly, combinations incorporating cyclophosphamide or uracil–tegafur showed variable results without clear superiority.

More intensive regimens, such as the addition of carboplatin, have demonstrated higher PSA response rates (68–95%) and median overall survival ranging from approximately 18 to 27 months. However, these benefits were offset by increased hematologic toxicity, including anemia, leukopenia, and thrombocytopenia, often requiring supportive measures such as granulocyte colony-stimulating factor.

Overall, while multiple combination strategies have been explored, most have not demonstrated a clear or consistent advantage over the estramustine–docetaxel doublet. Treatment intensification appears to increase toxicity without providing substantial additional clinical benefit.

Estramustine and docetaxel versus mitoxantrone

Mitoxantrone in combination with prednisone or hydrocortisone was historically regarded as a standard treatment for castration-resistant prostate cancer (CRPC), primarily providing symptomatic benefit without a clear survival advantage. This established benchmark prompted investigations into whether combination chemotherapy with estramustine and docetaxel could improve clinical outcomes.

Evidence from randomized phase II studies suggests increased activity with the estramustine–docetaxel combination compared with mitoxantrone-based therapy [48]. In an additional phase II study, 30 patients initially received three cycles of mitoxantrone (10 mg/m² on day 1) plus prednisone (10 mg daily), followed by treatment with estramustine (280 mg three times daily on days 1–5) and docetaxel (75 mg/m² on day 2) [50]. The prostate-specific antigen (PSA) response rate increased from 23% during mitoxantrone-based therapy to 63% following transition to estramustine–docetaxel. While these findings suggest improved antitumor activity, the non-randomized sequential design limits direct comparative interpretation.

A more definitive comparison was provided by a large phase III randomized trial [51]. In this study, 674 patients with metastatic castration-resistant prostate cancer were assigned to receive either estramustine (280 mg three times daily on days 1–5) plus docetaxel (60 mg/m² on day 2) or mitoxantrone (12 mg/m² on day 1) plus prednisone (10 mg daily), administered in 21-day cycles. The estramustine–docetaxel combination demonstrated a statistically significant, albeit modest, improvement in overall survival (17.5 vs 15.6 months). Median time to progression was also prolonged (6.3 vs 3.2 months, $p < 0.001$), and PSA response rates were higher (50% vs 27%, $p < 0.001$).

However, these benefits were accompanied by increased toxicity. Patients receiving estramustine–docetaxel experienced higher rates of neutropenic fever, gastrointestinal adverse effects, and cardiovascular events. These findings highlight the need to balance improved efficacy against the risk of treatment-related complications when considering this regimen in clinical practice. It is also noteworthy that the docetaxel dose used in this study (60 mg/m²) was lower than that employed in many earlier phase II trials (typically 70–75 mg/m²), which may influence interpretation of efficacy outcomes. A meta-analysis has suggested that prophylactic anticoagulation may be warranted in patients receiving estramustine-containing regimens due to an increased risk of thromboembolic events, although this risk does not appear to be clearly dose-dependent.

Contribution of estramustine to the efficacy of docetaxel-based therapy

The clinical value of adding estramustine to docetaxel in the treatment of castration-resistant prostate cancer (CRPC) has

been questioned [45,52–54]. Specifically, it remains uncertain to what extent estramustine contributes to the overall efficacy of combination therapy compared with docetaxel alone.

This question has been addressed in randomized phase II studies. In one such trial, 92 patients were assigned to receive 21-day cycles of either docetaxel alone (75 mg/m² on day 1) or docetaxel (70 mg/m² on day 2) combined with estramustine (280 mg twice daily on days 1–5) [55]. A prostate-specific antigen (PSA) response (≥50% decline) was observed in 30% of patients treated with docetaxel alone, compared with 68% in the combination arm ($p < 0.05$). Median time to progression was prolonged (2.9 vs 5.7 months), and median overall survival showed a modest increase (17.8 vs 19.3 months). Toxicity profiles were comparable between groups, with predominantly mild hematologic and non-hematologic adverse effects.

Similar findings were reported in another randomized phase II study, available in abstract form [56]. In this study, PSA response rates were 43% with docetaxel alone and 70% with the addition of estramustine. Progression-free survival was also improved (20 vs 30 weeks), supporting a potential additive effect of estramustine. Collectively, these studies indicate that the addition of estramustine to docetaxel is associated with improved PSA response rates and delayed disease progression. However, these trials were not powered to detect differences in overall survival, and the observed survival benefit remains modest.

To further explore the impact of estramustine on clinical outcomes, a meta-analysis of individual patient data was conducted [57]. This analysis included 603 patients with CRPC treated with either antimicrotubule-based chemotherapy alone (n = 304) or in combination with estramustine (n = 299). With a median follow-up of 2.8 years, overall survival was significantly improved in the estramustine-containing group ($p = 0.008$), corresponding to an absolute survival benefit of approximately 9.5% at one year. PSA response rates were also higher (52% vs 27%, $p < 0.0001$), and time to PSA progression was significantly prolonged ($p = 0.01$).

The meta-analysis also highlighted important safety considerations. The incidence of grade 3-4 thromboembolic events was significantly higher in patients receiving estramustine-containing regimens (6% vs 0.4%, $p = 0.02$). Conversely, a reduction in severe neutropenia was observed (6% vs 15%, $p = 0.002$).

Overall, these findings suggest that estramustine may enhance the antitumor activity of docetaxel-based chemotherapy, particularly in terms of biochemical response and disease control. However, the clinical relevance of this benefit must be weighed against the increased risk of thromboembolic complications. Furthermore, the optimal dosing schedule and patient selection criteria for estramustine-containing regimens remain to be clearly defined

Other combination strategies involving estramustine

In addition to its antimicrotubular activity, estramustine has been shown to disrupt the nuclear matrix in target cells [25]. This property provides a rationale for combining estramustine with etoposide, a topoisomerase II inhibitor that also acts at the level of the nuclear matrix. Preclinical studies have demonstrated synergistic inhibition of prostate cancer cell growth with this combination, both in vitro and in vivo [58], supporting its subsequent clinical evaluation.

Several phase II studies have investigated the combination of estramustine and etoposide (EE) in patients with castration-resistant prostate cancer (CRPC) (Table 3). In an initial study by Pienta et al. 42 patients received etoposide (50 mg/m²/day) and estramustine (15 mg/kg/day) for three weeks followed by a one-week rest period [59]. Among patients with measurable disease, objective responses were observed, including complete responses in three patients and partial responses in six patients. A prostate-specific antigen (PSA) response was reported in approximately 50% of patients overall and in 58% of those with bone metastases. However, treatment was associated with considerable toxicity, particularly nausea and leukopenia.

In a subsequent phase II study, the estramustine dose was reduced to 10 mg/kg/day [60]. Among 62 patients, the PSA response rate was 39%, with grade 3–4 toxicities primarily attributable to etoposide, including anemia, leukopenia, and thrombocytopenia. These findings suggested that lower-dose estramustine may maintain activity while reducing toxicity.

A later multicenter phase II study reported more modest efficacy, with a PSA response rate of 22% among patients receiving at least two treatment cycles [61]. Notably, treatment-related toxicity remained significant, including two treatment-related deaths, underscoring safety concerns associated with higher-dose regimens.

Subsequent studies have evaluated lower-dose estramustine (280–560 mg/day) in combination with etoposide [62-65]. These regimens were generally better tolerated and achieved PSA response rates ranging from 43% to 58%, suggesting a more favor-

Table 3. Summary of Phase II trials evaluating estramustine in combination with etoposide in CRPC

Study (Ref)	Patients (n)	Regimen	PSA Response ≥50%	Survival / Outcome	Toxicity	Key Findings
Pienta et al. [59]	42	Etoposide + EMP (high dose)	~50%	—	High	Active but toxic
Pienta et al. [60]	62	Reduced EMP dose	39%	—	Moderate	Lower toxicity, similar efficacy
Pienta et al. [61]	53	Same regimen	22%	—	Significant	Confirms toxicity concerns
Low-dose studies [62–65]	—	EMP 280–560 mg/day + etoposide	43–58%	—	Better tolerated	Favorable balance
Berruti et al. [66]	46	Etoposide + EMP	54%	OS 18.4 mo	Moderate	Comparable to taxane combos

able balance between efficacy and toxicity.

In a phase II study with extended follow-up, 46 patients treated with etoposide (100 mg/day) and estramustine (560 mg/day) demonstrated a PSA response rate of 54%, with a median time to progression of 7.4 months and median overall survival of 18.4 months [66]. While these outcomes are comparable to those reported for estramustine–docetaxel combinations in some studies, the absence of randomized comparisons limits definitive conclusions regarding relative efficacy.

Estramustine has also been explored in a variety of other combination regimens. A randomized phase II study evaluating multiple treatment strategies in 150 patients identified a regimen of weekly paclitaxel, estramustine, and carboplatin followed by sequential chemotherapy as a potentially active approach [67]. However, these findings remain exploratory and require validation in larger, controlled trials.

Overall, while estramustine-based combination therapies—particularly with etoposide-demonstrate clinical activity in CRPC, their role remains limited by toxicity and the lack of robust comparative data. Further studies would be required to define their place in contemporary treatment algorithms.

Other modifications of estramustine application

Estramustine has also been evaluated in alternative therapeutic settings, including monotherapy, modified dosing schedules, and neoadjuvant strategies.

Reassessment of estramustine monotherapy in metastatic castration-resistant prostate cancer (CRPC) has demonstrated limited but measurable activity. In a study by Hirano et al. a prostate-specific antigen (PSA) decline of ≥50% was observed in approximately 24% of patients, while responders demonstrated a cancer-specific survival rate of 83% at two years. Similar findings have been reported by Kitamura et al. with objective response rates ranging from 35% to 82% across different study populations and time points. These data suggest that while monotherapy activity is modest, selected patients may derive clinical benefit.

Various modifications of estramustine use have been explored, including first- and second-line therapy, intermittent high-dose schedules, and incorporation into combination regimens. Dosing strategies have varied considerably across studies, particularly in combination with docetaxel, where regimens have included docetaxel at 70-75 mg/m² every three weeks and estramustine administered in schedules ranging from intermittent multi-day dosing (e.g., days 1-5 and 8-12) to continuous daily administration.

Across these studies, combination therapy with docetaxel and estramustine has generally demonstrated higher PSA response rates and longer progression-related outcomes compared with docetaxel alone, with reported PSA response rates ranging from approximately 40% to 68% and progression times of 4.5 to 7.5 months. However, these findings should be interpreted cautiously due to heterogeneity in study design, dosing schedules, and patient populations.

Despite ongoing debate regarding its clinical role, estramustine continues to demonstrate potential utility, particularly in selected combination regimens. The variability in outcomes underscores the need for more standardized treatment approaches and better-defined patient selection criteria.

A distinct application of estramustine has been explored in the neoadjuvant setting for high-risk, non-metastatic, locally advanced prostate cancer. Studies by Hussain et al. and Prayer-Galetti et al. evaluated the combination of docetaxel and estramustine in patients with high-risk features, including clinical stage ≥T2b, PSA >15 ng/mL, and/or Gleason score ≥8. These studies reported feasible treatment administration and encouraging antitumor activity. However, the absence of randomized controlled data limits definitive conclusions, and further investigation is required to establish the role of this approach.

Overall, while multiple alternative applications of estramustine have been explored, their clinical relevance remains uncertain in the absence of robust comparative evidence.

Adverse reactions to estramustine

Gastrointestinal toxicity, particularly nausea and vomiting, is among the most commonly reported adverse effects associated with estramustine therapy. These reactions appear to be dose-dependent and are more frequent at higher dose levels. Supportive management with oral antiemetics, such as prochlorperazine, has been used in clinical practice. At daily doses of 560 mg or lower, gastrointestinal toxicity is generally mild and well tolerated.

Estramustine has also been associated with an increased risk of cardiovascular and thromboembolic events. In a phase III trial comparing docetaxel plus estramustine with mitoxantrone plus prednisone, cardiovascular events were reported in 15% of patients receiving the estramustine-containing regimen, compared with 7% in the control group [51]. Although this increased incidence was not associated with higher treatment-related mortality or discontinuation rates, it represents a clinically relevant safety concern.

Prophylactic anticoagulation, including low-dose warfarin or acetylsalicylic acid, has been explored in patients receiving estramustine-based therapy. However, evidence supporting routine prophylaxis remains limited, and the decision to initiate anticoagulation should be individualized based on patient-specific risk factors.

Given these safety considerations, caution is warranted when prescribing estramustine in patients with a history of cardiovascular disease or thromboembolic events. Careful risk assessment and monitoring are essential when incorporating estramustine into treatment regimens.

Conclusions

The introduction of taxane-based chemotherapy marked a significant advance in the treatment of castration-resistant prostate cancer (CRPC), with docetaxel-based regimens demonstrating a survival benefit over earlier therapies such as mitoxantrone. The addition of estramustine to docetaxel has been shown to improve biochemical response rates and delay disease progression in several clinical studies, although the overall survival benefit appears modest and is accompanied by an increased risk of adverse events, particularly thromboembolic and cardiovascular complications.

While estramustine-containing combinations exhibit antitumor activity, their role in contemporary clinical practice remains

limited. The balance between efficacy and toxicity, along with the availability of newer therapeutic agents, has reduced the routine use of estramustine in standard treatment algorithms. Nevertheless, estramustine may retain a role in selected patients, particularly in combination regimens where alternative options are limited or contraindicated.

The combination of estramustine with etoposide represents an additional therapeutic approach that has demonstrated clinical activity in phase II studies, with manageable toxicity in lower-dose regimens. However, the absence of randomized comparative trials limits definitive conclusions regarding its relative efficacy compared with taxane-based combinations.

Overall, estramustine remains a pharmacologically distinct agent with demonstrated activity in CRPC, particularly in combination with microtubule-targeting agents. Future research should focus on defining its optimal dosing strategies, identifying patient populations most likely to benefit, and clarifying its role within the evolving landscape of prostate cancer therapy.

Clinical Practice Implications

In the current therapeutic landscape of castration-resistant prostate cancer (CRPC), shaped by the widespread use of androgen receptor–targeted agents such as abiraterone acetate and enzalutamide, the clinical role of estramustine has become more limited and selective.

Estramustine-containing regimens, particularly in combination with docetaxel, demonstrate improved biochemical response rates and delayed disease progression; however, these benefits are modest and must be balanced against an increased risk of thromboembolic and cardiovascular complications. Consequently, estramustine is no longer part of standard first-line treatment strategies.

In clinical practice, estramustine may still be considered in selected situations:

• In later-line treatment settings as part of combination chemotherapy

• In patients with limited therapeutic alternatives or contraindications to standard agents

• As an individualized option where potential benefit outweighs toxicity risks

Treatment should be tailored carefully, given the lack of standardized dosing regimens and variability across studies. Dose adjustments and intermittent schedules may improve tolerability, particularly in patients experiencing gastrointestinal toxicity.

Due to the elevated risk of thromboembolic events, careful patient selection is essential. Thromboprophylaxis may be considered in high-risk individuals but should be applied on an individualized basis rather than routinely.

The use of estramustine in neoadjuvant settings or in combination with modern androgen receptor–targeted therapies remains investigational and is not currently supported by robust evidence.

Overall, estramustine should be regarded as a secondary or adjunctive option in CRPC management, with its use guided by patient-specific factors and the availability of more effective and better-tolerated therapies.

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