Estramustine Potentiates Taxane in Prostate and Refractory Breast Cancers

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Introduction

Estramustine (Emcyt) is nornitrogen mustard linked to estradiol. The original concept behind the design of the drug was that the estradiol could be used as a vehicle to deliver the alkylator into tumor cells that expressed estrogen receptors. It is now clear, however, that modified estrogens such as estramustine exert very little alkylating activity, and that they act primarily as antitubulins.[1]

Estramustine binds to tubulin and to microtubule-associated proteins, depolymerizes cytoplasmic microtubules, and disrupts the nuclear matrix.[2-4] Of uncertain clinical relevance, it is also an inhibitor of p-glycoprotein, the multidrug resistance protein.[5]

Estramustine has been most extensively studied as an oral agent. While the half-life of the parent compound, estramustine phosphate, is approximately 2 hours, the half-lives of the active metabolites estramustine and estromustine range from 50 to 100 hours.[6] The drug is usually administered in split daily doses to minimize nausea.

Hormone-Refractory Prostate Cancer

Estramustine as Single Agent

As a single agent, estramustine was studied in a placebo-controlled, double-blind, randomized study by the Danish Prostatic Cancer Group.[7] Of 131 patients with hormone-refractory prostate cancer, 129 were evaluable. Patients were randomized to receive oral estramustine phosphate (n = 61), administered continuously at the dose of 280 mg bid, or placebo (n = 68) using the same schedule.

The most valuable results of this study lie in the placebo-controlled evaluation of estramustine’s toxicity profile. Nausea and vomiting were experienced by 26 out of 61 (43%) of the estramustine patients, and considered severe in 8 out of 61 patients (13%). In the placebo group, however, this toxicity was experienced by 21 out of 68 (31%) patients and was severe in 9 out of 69 (13%). This suggests that a large proportion of the nausea and vomiting seen with this agent at this dose is related to pill taking or is anticipatory.

The only other toxicity seen in more than 10% of patients was breast tenderness or gynecomastia, which occurred in 25% of estramustine patients and 1% of those receiving placebo. One patient in the estramustine group had a pulmonary embolism, and no cases of deep vein thrombosis were reported.

In terms of efficacy, this study reinforced the common wisdom that prostate cancer is essentially chemo-resistant. No objective responses were observed and no differences in time to disease progression or survival were seen between estramustine and placebo.

There was a suggestion of activity with estramustine using PSA (prostate-specific antigen) criteria, however. Of 94 patients whose baseline PSA was at least twice the normal level, 16 out of 43 (37%)
in the estramustine group had a $\geq 50\%$ reduction in PSA (PSA-50), while only 1 out of 51 (2\%) patients in the placebo group displayed such a response.

**Taxanes as Single Agents**

Like estramustine, the taxanes exert their antitumor effect by targeting the microtubular apparatus. Paclitaxel (Taxol) and docetaxel (Taxotere) polymerize the microtubules, but additionally inhibit Bcl-2 and Bcl-xL by phosphorylation. These agents thus induce G2M arrest and apoptosis.[8]

Studies have shown that paclitaxel as a single agent is essentially ineffective against prostate cancer. In a phase II study performed by the Eastern Cooperative Oncology Group (ECOG), 23 patients with hormone-refractory prostate cancer received paclitaxel as a 24-hour infusion at doses ranging from 135 to 170 mg/m$^2$. One patient (4\%) had an objective response, and was the only one to have a response by PSA-50 criteria.[9]

In contrast, docetaxel has modest activity as a single agent in this disease. Preliminary results of two phase II studies of docetaxel at 75 mg/m$^2$ given every 3 weeks in hormone-refractory prostate cancer have been reported. In a study reported by Picus et al of 35 patients, 20\% had an objective response, and 46\% had a response by PSA-50 criteria.[10] Friedland et al studied 21 patients, and reported a 5\% objective response rate and PSA-50 responses in 33\%.[11]

**Synergistic Action of Taxanes and Estramustine Combined**

The modest activity of the taxanes and of estramustine as single agents in hormone-refractory prostate cancer clearly provides little rationale for combining them for use in this disease. When combined in vitro, however, the antitubulin activity of these agents is synergistic, with estramustine acting as a modulator of the taxane.[12]

Phase II studies of combined estramustine and paclitaxel (Table 1), [13,14] and combined estramustine and docetaxel (Table 2) [15-18] in hormone-refractory prostate cancer have been reported. These combinations have resulted in impressive objective (11\%-27\%) and PSA-50 (39\%-82\%) response rates in this disease and warrant further investigation. Although these data are from single-institution phase II studies, and the schedules of both estramustine and the taxanes vary significantly, indirect comparison of these results with those from single-agent studies suggests that the demonstrated in vitro synergism of these agents may indeed be clinically relevant.

**Metastatic Breast Cancer**

Two studies have assessed the role of estramustine in combination with a taxane in metastatic breast cancer (Table 3). Garcia et al reported a 20\% response rate in 18 evaluable breast cancer patients entered in a phase I study of paclitaxel and estramustine.[19] All of the patients had previously received paclitaxel. Talbot et al reported a 25\% response rate in a phase II study of combined docetaxel and estramustine in patients with metastatic breast cancer. Interestingly, the same response rate was observed in patients both with and without previous paclitaxel exposure.[20] As in prostate cancer, these data suggest that in breast cancer, estramustine is an effective modulator of taxanes.

**Thromboembolic Events**

Thromboembolic events complicate the course of approximately 10\% of patients treated with combined estramustine and taxanes. Although not a prominent toxicity in the single-agent estramustine studies, thromboembolic events are more likely related to the estrogen moiety of the estramustine than to any synergism between the two agents. This complication was documented in studies of both prostate and breast cancer, and at all doses and schedules of estramustine, with the exception of the study by Sinibaldi et al,[18] in which all patients received prophylactic warfarin (Coumadin) with excellent effect.
New Strategies Needed

New strategies are required to improve the toxicity profile of the estramustine/taxane combination if it is to become a part of routine oncology practice. The most appealing option to minimize toxicities is simply to reduce the dose. As estramustine is being given as a modulator of taxanes rather than as an antineoplastic agent in its own right, it may not be necessary to administer it at the maximum tolerated dose to achieve the required biological effect. If lower doses can modulate the taxanes as effectively as doses that have been studied to date (generally 600-840 mg/d in prostate cancer and approximately 1,500 mg/d in breast cancer), it may be possible to abrogate toxicities without further intervention.

The problem of nausea and vomiting is already being addressed. An intravenous formulation of estramustine is now in clinical development. It appears to be associated with less nausea than the oral formulation, and can be administered once per cycle on the same day as the chemotherapy. Intravenous estramustine is now being incorporated into combinations with taxanes and with vinorelbine (Navelbine), and will probably eventually replace the oral preparation in the clinic.

The study by Sinibaldi et al demonstrates that thromboembolic complications can be minimized with the use of prophylactic oral anticoagulation.[18] Low-dose warfarin should therefore be considered in all studies using estramustine at daily doses of 600 mg or higher.

In hormone-resistant prostate cancer, combinations of taxanes and estramustine offer clinically significant activity in a disease that was, until recently, effectively untreatable. These combinations are now being compared in front-line phase III studies (eg, SWOG 9916) against the combination of mitoxantrone (Novantrone) and prednisone.

Estramustine with vinorelbine has also been tested in patients with hormone-resistant prostate cancer, again with promising results.[21] The activity of estramustine with single-agent antitubulins thus provides a strong rationale for the development of triplets comprising a taxane, vinorelbine, and estramustine. A phase I study of paclitaxel, vinorelbine, and estramustine, which is being conducted at New York University Medical Center, will soon be completed. A report on the study is to be made at the American Society of Clinical Oncology (ASCO) meeting in May 2001 (Sewak et al). A phase II study will follow in hormone-refractory prostate cancer.

In metastatic breast cancer, combinations of estramustine and taxanes have moderate activity in taxane-pretreated populations, but the toxicity profile of the combination currently limits its development in this disease, which has a far broader range of therapeutic options available.

Finally, although initially developed for use in hormone-responsive tumors, estramustine, as a modulator should theoretically be effective in any tumor with sensitivity to antitubulins. Thus estramustine/antitubulin combinations may have a role in tumors originating in sites other than the prostate and breast, including lung, head and neck, ovary, endometrium, and bladder.

References:


