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ORIGINAL ARTICLE

Chemotherapy plus estramustine for management of castration-resistant prostate cancer: Meta-analysis of randomized controlled trials☆

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KEYWORDS
Prostate cancer;
Estramustine;
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Abstract

Objective: Estramustine, an agent with both hormonal and non-hormonal effects in men, is supposed to be effective in treating castration-resistant prostate cancer. However, previous studies have reported conflicting results. We conducted this meta-analysis to evaluate the efficacy and toxicity of additional estramustine to chemotherapy.

Methods: Data sources including PubMed, Medline, EMBASE, and Cochrane Controlled Trials Register were searched to identify potentially relevant randomized controlled trials. Prostate specific antigen (PSA) response, overall survival, and grades 3–4 toxicity were analyzed.

Results: Seven randomized controlled trials, a total of 839 patients, were enrolled. The pooled odds ratio for PSA response was 3.02 (95% CI = 1.69–5.39, $p = .0002$); the pooled hazard ratio for overall survival was .95 (95% CI = .80–1.14, $p = .58$); the pooled odds ratio for nausea/vomiting and cardiovascular toxicity were 3.90 (95% CI = 1.05–14.45, $p = .04$) and 2.22 (95% CI = 1.15–4.30, $p = .02$). No significant difference was detected for neutropenia, anemia, thrombocytopenia, diarrhea, fatigue, or neuropathy ($p > .05$).

Conclusions: According to this meta-analysis, chemotherapy with additional estramustine increased the PSA response rate. However, it increased the risk of grade 3 or 4 adverse effects such as nausea/vomiting and cardiovascular events, and the overall survival was not improved for castration-resistant prostate cancer patients.

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PALABRAS CLAVE
Cáncer de próstata;
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Metaanálisis

Quimioterapia con estramustina en el manejo del cáncer de próstata resistente a la castración: metaanálisis de ensayos controlados aleatorizados

Resumen

Objetivo: La estramustina, un agente con efectos tanto hormonales como no hormonales en los hombres, se supone que es eficaz en el tratamiento de cáncer de próstata resistente

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a la castración. Sin embargo, estudios previos han notificado resultados contradictorios. Hemos llevado a cabo este metaanálisis para evaluar la eficacia y la toxicidad de estramustina adicional a la quimioterapia.
Métodos: Se realizaron búsquedas en las bases de datos, incluyendo PubMed, Medline, EMBASE y Cochrane Controlled Trials Register, para identificar los ensayos controlados aleatorizados potencialmente relevantes. Se analizaron la respuesta del antígeno prostático específico (PSA), la supervivencia global y la toxicidad de grado 3 a 4.
Resultados: Siete ensayos controlados aleatorizados, un total de 839 pacientes, fueron incluidos. La *odds ratio* combinada para la respuesta de PSA fue de 3,02 (IC 95% = 1,69-5,39, p = 0,0002); el cociente de riesgos instantáneos agrupado de supervivencia global fue de 0,95 (IC 95% = 0,80-1,14, p = 0,58); la *odds ratio* combinada para náuseas/vómitos y toxicidad cardiovascular fue de 3,90 (IC 95% = 1,05-14,45, p = 0,04) y 2,22 (IC 95% = 1,15-4,30, p = 0,02). No se detectó ninguna diferencia significativa para neutropenia, anemia, trombocitopenia, diarrea, fatiga o neuropatía (p > 0,05).
Conclusiones: Según este metaanálisis la quimioterapia con estramustina adicional aumentaba la tasa de respuesta del PSA. Sin embargo, aumentaba el riesgo de efectos adversos de grado 3 o 4 como náuseas/vómitos y los episodios cardiovasculares, y la supervivencia global no mejoró en los pacientes con cáncer de próstata resistente a la castración.
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Background

Prostate cancer is the second most common malignant neoplasm and a significant cause of death by cancer in men.[1] It is estimated that there were more than 240,000 new cases and 28,000 deaths due to prostate cancer in the United States in 2012.[2] Huggins et al.[3] demonstrated the androgenic dependence of prostate cancer more than 70 years ago, and since then androgen deprivation therapy has been increasingly applied to metastatic and recurrent prostate cancer, as well as to locally advanced disease.[4,5] Although symptomatic improvement and control of the disease can be achieved in 80–90% of men, all patients with advanced prostate cancer will in time become castration-resistant 18–24 months after the primary androgenic ablation.[6] For these patients, the prognosis is negative and the median life expectancy is 12–18 months after becoming castration-resistant.[7] The treatment options for men with castration-resistant prostate cancer (CRPC) are very limited. Chemotherapy has been shown to improve overall survival, progression-free survival and quality of life.

Chemotherapy based on docetaxel and cabazitaxel can extend median survival from 2.5 to 3 months.[8,9] Additionally, cytotoxic agents are employed to relieve symptoms and extend survival.[8] However, the impact of these drugs is modest, which suggests the need for improved therapy for CRPC.

Estramustine is a combination of mustard, nitrogen and 17 β-estradiol, with both hormonal and nonhormonal effects in men. Clinically employed as estramustine phosphate, estramustine reduces serum testosterone levels and inhibits microtubule dynamics by binding to tubulin and microtubule-associated proteins.[10] After its absorption in the gastrointestinal tract, estramustine is metabolized into estrone and estradiol, which are distributed preferentially in the prostate tissue.[11] They are therefore able to selectively interrupt prostate cancer cells and cause the inhibition of mitosis at the expense of increasing the adverse effects such as anemia, nausea, vomiting, fatigue and cardiovascular toxicity.[12] Estramustine has been employed to treat CRPC for many years with limited effect as a single agent. However, a synergistic effect can be achieved when combined with other chemotherapy agents, especially with other microtubule inhibitors, in order to increase overall survival for patients with prostate cancer. This hypothesis was supported in a number of *in vitro* models and clinical trials, while others showed no significant differences.[13,14] Therefore, we have performed this meta-analysis to evaluate and compare the efficacy and toxicity of estramustine added to chemotherapy for the treatment of CRPC.

Materials and methods

Data resources

The data resources were limited to controlled, randomized prospective trials in the last 20 years (1993–2013). Searches were performed on PubMed, EMBASE and the Cochrane Central Register of Controlled Trials using the following search terms: (1) prostatic neoplasms; (2) estramustine. Additionally, reference lists of all previous primary articles and systematic reviews were analyzed to obtain information on additional trials. The latest search was conducted on April 11, 2013.

Study selection and quality assessment

Two reviewers (CZ and TJ) independently evaluated the study titles and abstracts for possible selection. The full text of the corresponding articles was then reviewed. The trials were considered eligible if they met the following requirements: (1) The patients were diagnosed with prostate adenocarcinoma; (2) progressive diseases were observed despite androgenic ablation; (3) patients were randomly assigned to different treatment arms; (4) a chemotherapy (control) group was compared to the same regimen plus estramustine (experimental) group; and (5) at least one of the outcome measures was reported.

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