RESEARCH ARTICLE

Lenalidomide in Treating Patients with Castration-Resistant Prostate Cancer

Dong-Liang Xing[1], Dong-Kui Song[2]*, Li-Rong Zhang[3]

Abstract

Background: This analysis was conducted to evaluate the efficacy and safety of lenalidomide based regimen in treating patients with castration-resistant prostate cancer. Materials and Methods: Clinical studies evaluating the efficacy and safety of lenalidomide based regimens on response and safety for patients with castration-resistant prostate cancer were identified using a predefined search strategy. A pooled response rate (rate of PSA level decline of ≥50%) to treatment was calculated. Results: In lenalidomide based regimen, 3 clinical studies which including 98 patients with castration-resistant prostate cancer were considered eligible for inclusion. These lenalidomide based regimens included cisplatin, doxorubicin, or GM-CSF. Pooled analysis suggested that, in all patients, the pooled PSA level decline of ≥50% was 13.3% (13/98) in lenalidomide based regimens. Fatigue, nausea and vomitting were the main side effects. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in patients with lenalidomide based regimens. Conclusions: This evidence based analysis suggests that lenalidomide based regimens are associated with mild response rate and acceptable toxicities for treating patients with castration-resistant prostate cancer.

Keywords: Lenalidomide - castration-resistant prostate cancer

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Introduction

Prostate cancer is one of the most common cancer of male Chinese (Du et al., 2014). For patients with metastatic or recurrent prostate cancer, androgen-deprivation therapy is considered the first-line therapy to reduce morbidity and improve survival (Messing et al., 1999). The management of castration-resistant metastatic prostate cancer after androgen-deprivation therapy remains a major clinical challenge, because of symptoms and progressive decline in performance status in this group of patients. Chemotherapy is considered an effective treatment for patients with metastatic castration-resistant prostate cancer in China since 2000. And the important evidence in this field is the results from two randomized phase III clinical trials suggesting an overall survival benefit with docetaxel (Ferrero et al., 2004; Baker et al., 2004). Thus, the US FDA-approved docetaxel for patients with castration-resistant prostate cancer and the commonly used dosage is 75 mg/m^2 given intravenously over 1 hour every 21 days on day 1 (Pazdur et al., 2013). Other clinical administration of docetaxel that could be considered includes 50 mg/m^2 every 2 weeks (Kellokumpu-Lehtinen et al., 2013). Because a comparison of weekly docetaxel pharmacokinetics with triweekly administration demonstrated similar results, weekly dosage could be considered at 35 mg/ m^2, 36 mg/ m^2, or 40 mg/m^2 intravenously weekly for 6 weeks (Hurria et al., 2013; Berry et al., 2001; Ferrero et al., 2004; Baker et al., 2004).

In recent years, the therapeutic regimens for castration-resistant prostate cancer are rapidly evolved and there are several other commonly used agents, including enzalutamide, abiraterone acetate, cabazitaxel, radium-223 and sipeleucel-T, demonstrated to extend OS in randomized phase III trials (Kantoff et al., 2010; Kantoff et al., 2010; de Bono et al., 2011; de Bono et al., 2010; Scher et al., 2012; Parker et al., 2013). And, lenalidomide is an oral thalidomide analogue with antiangiogenic and antineoplastic properties that is approved for myelodysplasia and multiple myeloma. In addition to the antiangiogenic activity, lenalidomide has substantial anti-inflammatory and immunomodulatory properties (Nabhan et al., 2012).

According to this background, we hypothesize that lenalidomide originated treatment could be established as an optimal schedule for treating patients with castration-resistant prostate cancer.

Materials and Methods

Search strategy

We searched Medline, by using the following search terms: (lenalidomide) and (castration-resistant prostate

*[1]Department of Urology, the Fifth Affiliated Hospital of Zhengzhou University, [2]Department of Urology, the First Affiliated Hospital of Zhengzhou University, [3]Department of Pharmacogenetics, the Medical College of Zhengzhou University, Zhengzhou, China *For correspondence: dongkui_765@163.com*

cancer). All clinical studies evaluating the impact of lenalidomide on patients with castration-resistant prostate cancer. Published in English prior to December 1st of 2014 were identified. If samples of two studies overlap, only the latest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) clinical studies, combined with docetaxel or a platinum; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified prostate cancer and was castration-resistant, with serum PSA surveillance, or the presence of at least one bidimensionally measurable lesion, a performance status (WHO) 2, age 18 years. Studies were excluded if one of the following existed: (1) duplicate data; (2) no sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, and country of the first or corresponding author, the number of patients.

Results

There were 4 papers relevant to the search words. Via steps of screening the title and reading the abstract, 3 studies were identified (Keizman et al., 2010; Nabhan et al., 2014; Garcia et al., 2014) when lenalidomide was used in the treatment for patients with castration-resistant prostate cancer. All these studies had been carried out in the USA. The following outcomes were presented in at least all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (achieved PSA level decline) and toxicities.

Characteristics of lenalidomide as chemotherapy, studies included in this study are presented as short-term outcomes: the response rate of Nabhan et al. (2014) was 11%, of Garcia et al. (2014) was 12.5%, and of Keizman et al. (2010) was 18%. Totally, 98 patients were enrolled and 13 patients achieved PSA level decline of ≥50%, the pooled response rate thus was 13.3% (13/98).

Observation on toxicities included fatigue, nausea and vomitting were the main side effects. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in patients with lenalidomide based treatments.

Discussion

Prostate cancer contributes to approximately 30, 000 deaths annually in the USA (Siegel et al., 2013). For patients with metastatic prostate cancer, their disease will eventually develop to a stage defined as castration-resistant prostate cancer, after initially responding to androgen deprivation therapy (Nelson et al., 2003). Treatment for patients with castration-resistant prostate cancer includes docetaxel/paclitaxel based chemotherapy, but the median survival time for patients in this stage is estimated to be less than 2 years (Petrylak et al., 2004; de Bono et al., 2010; Kantoff et al., 2010; Luo et al., 2013).

Lenalidomide is an oral thalidomide analogue with antiangiogenic and antineoplastic properties that is approved for myelodysplasia and multiple myeloma. In addition to its antiangiogenic activity, lenalidomide has substantial anti-inflammatory and immunomodulatory properties (Nabhan et al., 2012). lenalidomide was tested by previous phase II trials for patients with nonmetastatic biochemically relapsed prostate cancer (Keizman et al., 2010). In a study published in 2010, Keizman et al. conducted a phase 2 study to assess the efficacy and safety of lenalidomide at 5 or 25 mg/d in patients with nonmetastatic biochemically relapsed prostate cancer who were previously untreated for metastatic disease (Keizman et al., 2010). They treated 60 patients and all patients were stratified by prostate specific antigen doubling time, surgery/radiation therapy, prior androgen deprivation therapy, and than patients were randomized to lenalidomide 5 mg (n=26) or 25 mg/d (n=34) for 3 weeks repeated monthly for 6 months or until dose limiting toxicity or disease progression. Changes in PSA slopes were calculated using the regression of the log PSA for each patient before and during the initial6 months (Keizman et al., 2010). In their results, baseline variables of all patients were balanced between two arms. Grade 3/4 toxicity rates were 12% (n=3) with 5 mg and 29% (n=10) with 25 mg (p=0.1), and most commonly seen toxicity was neutropenia (5 patients, all in 25 mg arm). Two patients per arm had thromboembolic events. The change in PSA slope was greater with 25 mg versus 5 mg [-0.172 (-0.24 to -0.11) versus -0.033 (-0.11 to 0.04); *P*=0.005]. With a mean follow-up of 31.4 months (range 14-44), 5 patients on 25 mg and one patient on 5 mg remain on the study (Keizman et al., 2010). Thus, they concluded that lenalidomide has acceptable toxicity and is associated with long-term disease stabilization and PSA declines (Keizman et al., 2010).

In another study, Garcia et al. treated 32 patients with castration-resistant prostate cancer in an effort to evaluate the clinical and immune activity of granulocyte-macrophage colony-stimulating factor and lenalidomide (Garcia et al., 2014). Because granulocyte-macrophage colony-stimulating factor is a pleiotropic cytokine that stimulates dendritic cells (DCs) and promotes uptake of tumor antigens by DCs leading to T-cell cross-priming. And, lenalidomide is an immunomodulatory analog of thalidomide with significant T-cell stimulatory and

antiangiogenic properties. (Garcia et al., 2014). And, granulocyte-macrophage colony-stimulating factor in combination with thalidomide could induce prostate-specific antigen responses in 20% to 25% of patients with castration-resistant prostate cancer (Garcia et al., 2014). In this study, asymptomatic patients with castration-resistant prostate cancer were enrolled. All the patients received 250 g of granulocyte-macrophage colony-stimulating factor administered subcutaneously 3 times weekly along with 25mg/d of lenalidomide administered orally on days 1 to 21 of a 28-day cycle (Garcia et al., 2014). Their results suggested that although 81% of the patients achieved a decline in the levels of prostate-specific antigen while on therapy, only 4 achieved a prostate-specific antigen level decline of ≥50%. The overall response rate among 11 patients with response evaluation criteria in solid tumors-defined measurable disease was 18%. Overall toxicity was grade 1 and 2 and included fatigue observed in 69% of the patients, nausea/vomiting in 34%, and diarrhea in 28% of the patients. Grade 3 or 4 toxicities occurred in 22% of the patients and were primarily thrombocytopenia (9%) or neutropenia (19%) or both. Thus, they concluded that administration of granulocyte-macrophage colony-stimulating factor and lenalidomide in patients with castration-resistant prostate cancer is safe with modest evidence of antitumor activity (Garcia et al., 2014).

With a purpose to assess the antitumor activity and toxicity of lenalidomide, in patients with chemotherapy-naive, castration-resistant prostate cancer, Nabhan et al conducted a phase II study (Nabhan et al., 2014). They treated all patients with 25 mg/d lenalidomide for 21 days in 28-day cycles, until disease progression or unacceptable toxicity developed. In their results, of 32 patients enrolled, 77% (n=25) had Gleason scores ≥7. The median age was 74 years (58-89 y), the median prostate-specific antigen level was 66 ng/mL, and 5 of 32 patients (17%) had liver or lung involvement. The median number of lenalidomide cycles was 3. Stable disease was seen in 20 patients, therefore a clinical benefit rate of 63%. The median time to radiographic progression was 4 months; the median overall survival time was 20 months. Of 27 prostate-specific antigen evaluable patients, 13 (48%) had a decline in prostate-specific antigen level; 3 (11%) had >50% prostate-specific antigen decrease; the median time to prostate-specific antigen progression was 3 months. In this study, grade 3/4 hematologic toxicities were the most common adverse events without adverse impact on quality of life (Nabhan et al., 2014). Serious adverse events occurred in 14 patients (44%), including 1 patient (3%) with a rash definitely related to lenalidomide. Thus, they concluded that lenalidomide monotherapy was modest active in treating patients with chemotherapy-naive castration-resistant prostate cancer (Nabhan et al., 2014).

Our current study evaluated the efficacy and safety of lenalidomide based regimen in treating patients with castration-resistant prostate cancer. Our results suggested that in 98 patients with castration-resistant prostate cancer, the pooled prostate-specific antigen level decline of ≥50% was 13.3% (13/98) in lenalidomide based regimen. Fatigue, nausea and vomitting were the main side effects. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in patients with lenalidomide based regimens. Thus, we concluded that lenalidomide based regimens are associated with mild response rate and accepted toxicities for treating patients with castration-resistant prostate cancer.

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