Docetaxel plus prednisone for CRPC patients in mandarin Chinese population: Single Institute Experience

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ABSTRACT:

Introduction: Docetaxel (75mg/m² three weekly) with prednisone (5mg twice) has been remained one of the standard systemic therapy for CRPC patients. Despite the excellent antitumor effect of docetaxel as well as well tolerance in western CRPC patients, it is important to evaluate the adverse effect of docetaxel based chemotherapy in mandarin Chinese.

This study was undertaken to assess the effects of docetaxel in combination with prednisone in mandarin Chinese patients with CRPC.

Methods: 17 CRPC patients median age of 71[44-78] were included with 145 cycles of chemotherapy. Treatment consists of intravenous docetaxel 75mg/m² three weekly and oral prednisone 5mg twice a day, for maximum ten cycles of therapy. PSA response rate was evaluated with RACIST criteria as well as haematological adverse effects were noted.

Results: The total median cycle of chemotherapy given was 10. A PSA response (50% reduction in PSA from baseline) was seen in 66.67% (10 of 15 evaluable patients) at 6 cycles whereas 58.33 % (7 of 12 evaluable patients) at 10 cycles of chemotherapy. The patients that completed 10 cycles were 12(80%). The median PSA value after 10 and 6 cycles were 98.10[0.46-3538] and 46.6 [0.46-954]. With median follow up 13.8 months, OS was19months [95% CI 15.99-22.05].Hematological adverse events of (any grade) toxicity included neutropenia (26.6%), and febrile neutropenia (6.7%).

Conclusions: The effect of docetaxel in combination with prednisone was found effective with manageable adverse effect in Chinese with CRPC.

Keywords: castration resistant prostate cancer; docetaxel; PSA; prednisone

Introduction

The incidence of prostate cancer is increasing in the world, even in china recently [1]. Early disease can be treated by surgery or radiotherapy, but hormonal therapy is useful for advanced disease. However, 80% of prostate cancer is controlled by hormonal therapy for 1.5-3 years, later, even with castration; androgen prevails in 20 % and become CRPC which can be treated with chemotherapy [2].

In 2004, the results of two randomised trials (TAX327 and SWOG99-16) were published and both revealed significant benefits for CRPC patients treated with docetaxel and mitoxantrone, respectively [3,5]. Docetaxel (75-100 mg/m² in three weeks) with prednisone (5mg twice daily) alone in TAX327 showed significant length of overall survival and manageable adverse effects. However, these two studies results were based on heterogeneous western CRPC patients [3]. The purpose of the current study was to observe effects of docetaxel and prednisone in mainland Chinese patients with CRPC.

Methods:

This study was conducted retrospectively in the Department of Urology in the 1st affiliated Hospital of X’ian Jiaotong University from 2010 to 2013, China.

1) Inclusion criteria

(1) PSA value should increase twice the nadir value in 4 weeks apart test while in hormonal therapy
(2) The patients should be in castration state whether by medically or surgically with testosterone level <50 µ/ml
(3) Patients performance status (ECOG) lesser than 2
(4) The life expectancy with at least more than 6 months computed by nomogram
(5) The bone marrow function should be adequate with Hb 8gm/dl, WBC 4-10/dl, platelet count greater than 1,00,000 adequate liver function: liver enzymes and bilirubin and plasma albumin within our institute’s upper limit, alkaline phosphatases <2.5 times upper normal limit, adequate renal function ( S. creatinine <1.5 times upper normal limit)
(6) All patients provided with written consent before treatment
(7) Other treatment such as radiotherapy, radical prostatectomy, brachytherapy, hormonal therapy had been tried
(8) All pathological grade prostate cancer was included in the study [heterogeneous group]

2) Exclusion criteria

(1) Patients who had more than 10 cycles or less than 6 cycles of docetaxel-prednisone regime and treated CRPC with other chemotherapy except Estramustine
(2) Medical problems with severity including renal dysfunction, liver dysfunction, myocardial infarction, cardiovascular accident
(3) Severe medical problem patients

The total 17 patients with CRPC were given docetaxel and prednisone regime from January 2011 to April 2013. The treatment model included local heterogeneous CRPC patients. Patients received intravenous docetaxel (75mg/m2) in every 3 weeks plus prednisone (5 mg twice a day) through the entire course of treatment. Cycles were repeated every 21 days for at least 6th cycles. Treatment was continued until excessive toxicity or disease progression was noted. Prior to treatment, all patients had a detailed medical history, physical examinations, and baseline laboratory measurements performed. Pretreatment tumor status was evaluated using CT or magnetic resonance imaging (MRI), and bone scans when necessary. Patients were seen on day 1 of every treatment cycle for a brief history, physical examination, assessment of adverse events, complete blood count, testing of renal and liver function, and PSA levels. There was no earlier interval for tumor response imaging evaluation, but re-evaluations occurred after the 6th cycle or after clinical signs of disease progression.

Evaluation, response and toxicity

For patients with at least one lesion evaluable in two dimensions, response evaluation criteria in solid tumors (RECIST) were used. But, we used PSA levels to measure the progression and response. A PSA response was defined as a 50% decrease in PSA relative to pre-treatment levels sustained for at least one course of cycle. The PSA progression disease was defined as a > 50% increase in PSA from the PSA baseline. The National Cancer Institute common Terminology Criteria of Adverse Events (NCI-CTCAE, Version 4.0) were used to assess toxicity. Patients who had greater than grade II non-hematological toxicity (excluding alopecia and adequately treated GI upset) or grade III hematological toxicity the treatment was delayed or treated the complications secondary to hematological toxicity with G-CSF. Dose reduction for toxicity was done.

The data collected in our study include baseline biochemical parameters, prior therapies, first date of treatment, information about pain and GI upset after drug start, grading of prostate cancer, date of progression, PSA response after 6th cycle of chemotherapy, date of death or last follow up. Kaplan-Meier estimates and log rank test were used to analyze time event variable. All the tests were 1 sided and p value ≤ 0.05 was considered statistically significant. SPSS for windows IBM version 20.0 was used for statistical analysis.

Results

Fifteen of 17 CRPC patients who received docetaxel prednisone therapy met the eligibility criteria for enrolment into the study, and completed more than 6 cycles of chemotherapy. Twelve of 15 completed 10 cycles. Two of 17 were excluded from the study as one lost in the treatment course after taking 3 and other 2 cycles. One of 15 patients had 8 cycles of chemotherapy, afterward he was sent for radiotherapy as disease became progressive. Another 2 patients completed only 6 cycles.

Response of patients

The total median cycle of chemotherapy given was 10. A PSA response (50% reduction in PSA from baseline) was seen in 66.67% (10 of 15 evaluable patients) at 6 cycles of chemotherapy whereas 58.33% (7 of 12 evaluable patients) at 10 cycles of chemotherapy. The number of patients that complete 10 cycles of treatment was 12(80%). The median PSA value after 10 cycles was 98.10[0.46-3538] and median PSA value at 6 cycles was 46.6 [0.46-954]. With median follow up duration of 13.8 months, using Kaplan-Meier, median OS was 19 months [95% CI 15.99-22.05]. The details in table 2.

Toxicity

A total of 145 cycles of treatment were administered to 17 CRPC patients. Hematological adverse events of grade 2 or 3 toxicity were only found in study that includes neutropenia (26.6%), leucopenia (46.6%) and anemia (20%). One of 15 patients had febrile neutropenia (6.7%) who was admitted in hospital due to the development of fever and was treated with antibiotics and G-CSF. Neutropenia was developed a week after the docetaxel administered in second cycle. Patients’ refusal and disease progression were the only cause of discontinuation in chemotherapy. Two of 17 patients (11.6%) discontinued treatment due to refusal, whereas 1(6.67%) had disease progression at 8 cycles of therapy and was sent for radiotherapy. There were 3 deaths may be attributable to docetaxel treatment. No need to reduce dose of docetaxel during the treatment course. The details table 3.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no of case</td>
<td>17</td>
</tr>
<tr>
<td>Gleason score, %</td>
<td></td>
</tr>
<tr>
<td>≤ 7</td>
<td>11(73.3)</td>
</tr>
<tr>
<td>≥ 8 or 10</td>
<td>4(26.4)</td>
</tr>
<tr>
<td>Radical prostatectomy, %</td>
<td>5(33.3)</td>
</tr>
<tr>
<td>Orchectomy, %</td>
<td>12(80)</td>
</tr>
<tr>
<td>Baseline median WBC, $10^9$</td>
<td>5.1[3.70-13]</td>
</tr>
<tr>
<td>Baseline Alkaline phosphatase,</td>
<td>114[22-548]</td>
</tr>
</tbody>
</table>
U/L
Baseline hemoglobin, g/dL 11.90[8.70-15.50]
Baseline median PSA, ng/mL 123.6[8.35-2250]
Total no chemotherapy 145
Age, years 71[44-78]
BMI 23.39[20.2-30.7]

Performance status, %
0 8(53.3 %)
1 7(46%)

Drugs used, %
Bicalutamide 5(33.3 %)
Flutamide 2(13.3 %)
Bicalutamide/flutamide/Estra mustine 8(53.3 %)

Metastases, %
Bone 13(86%)%
Bone +visceral 3(20%)
Smoker, % 9(60%)
Alcohol ,% 3(20 %)
Mean ADT last for, months 30(10-72)

Pathological grade, %
Low grade 11(73.3)
Moderate 4(26.6)
High grade ND

Table 2 Response characteristics post docetaxel

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>current results</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of chemo cycles(median)</td>
<td>10 [2-10]</td>
</tr>
<tr>
<td>Median overall survival, months</td>
<td>19 [15.99-22.05]</td>
</tr>
<tr>
<td>50 % reduction in PSA at 10 cycles, %</td>
<td>7 (58.33 %)</td>
</tr>
<tr>
<td>50 % reduction in PSA at 6 cycle, %</td>
<td>10 (66.67 %)</td>
</tr>
<tr>
<td>Median lymphocyte, 10*9</td>
<td>10.3 [0.62-1.97]</td>
</tr>
<tr>
<td>Median WBC after 10 cycle, 10*9</td>
<td>6.6 [4.49-9.60]</td>
</tr>
<tr>
<td>Median Neutrophil after 10 cycle, 10*9</td>
<td>4.82 [3.12-6.76]</td>
</tr>
<tr>
<td>Median alkaline phosphatase, U/L</td>
<td>106 [71-274]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Current study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia [GM CSF use]</td>
<td>grade 3 or 4 %</td>
</tr>
<tr>
<td>Neutropenia, %</td>
<td>4(26.6)</td>
</tr>
<tr>
<td>Leucopenia, %</td>
<td>7(46.6)</td>
</tr>
<tr>
<td>Thrombocytopenia, %</td>
<td>0</td>
</tr>
<tr>
<td>Anemia grade 2 or 3 only, %</td>
<td>3(20)</td>
</tr>
<tr>
<td>Nail disorder, %</td>
<td>7(46.6)</td>
</tr>
<tr>
<td>Alopecia, %</td>
<td>11(73.3)</td>
</tr>
<tr>
<td>GI upset (nausea and vomiting, loss of appetite), %</td>
<td>4(26.6)</td>
</tr>
</tbody>
</table>

Figure 1 showing the overall survival

DISCUSSION

Although there are so many novel agents such as Cabazitaxel, Sipuleucel, Abiraterone, MDV 3100 etc. are on the process of phase III trial [6-11], and docetaxel is still a promising and first line drug in prostate cancer [CRPC] treatment. The docetaxels’ anti-tumor effect via stabilizing tubulin in androgen dependent as well as androgen independent prostate cancer line[4] was become a milestone for initiating two randomized trials, TAX327 and the SWOG-16 in 2004, which showed a survival benefit of
docetaxel in men with metastatic CRPC in western patients[3].
Our study was focused to observe the possible adverse effects of docetaxel in mandarin Chinese CRPC men. In terms of response among them, the PSA response 66.67% upto 6 cycles of treatment as well as PSA response 58.33% at the end of 10 cycles of treatment was comparatively much effective as to those TAX327[3] and SWOG-16 [5] that revealed PSA response 45% and 50%, respectively. The comparatively better result in PSA response in our study still has no simple explanation, but it may be contributed due to diverse in characteristics between two study such as patients’ diverse demographic characteristics, clinic-pathology (inclusion of high grade prostate cancer in TAX 327), Gleason score <7(42% in TAX327 vs73.3% in current study).

The median Overall Survival times of patients who received Docetaxel and prednisone every 3 weeks in the TAX 327 study were 18.9 months in the first report [3] and 19.2 months in the updated one published in 2008[12]. Although our study demonstrated concomitant median Overall Survival [figure 1]to the TAX 327 study [3], the reason for this result seemed to be less difference in PSA values between the two studies. The baseline median PSA values in the TAX 327 study and our study, while docetaxel and prednisone initiated, were 114 ng/ml and 123 ng/ml, respectively. Similarly, patients who started Docetaxel and Prednisone with a lower PSA value had longer Overall Survival than those with a higher one [13]. Thus, Docetaxel and prednisone should be started for CRPC in lower level of PSA. This is supported by the literature of Canadian Guideline of prostate cancer [level 1 Evidence, Grade A recommendation [14]. Armstrong et al. [15] reported that a 30% or more PSA reduction within 3 months was one of the prognostic factors that correlated with OS. Similarly, our study showed a good PSA reduction within cycle 6. Pond et al. [16] reported TAX 327 subgroup analysis of the association between the metastatic site and prognosis. The median Overall Survival times were worsened in the ascending order of the metastatic site: lymph node only, bone only, bone and lymph node, lung and liver in their report. They revealed that the site of the metastasis was an independent prognostic factor and visceral metastasis was unfavorable. Although our study showed similar results for OS, the metastatic site was not a significant prognostic factor. This result seemed to be associated with the small number of patients with visceral metastasis 3 of 15(20%) in our study, and their significantly lower PSA, thus the median OS times with TAX327 was concomitant with our study. Of men with PSA reduction ≥ 30% by 3 months after starting docetaxel and prednisone, 118 of 178(66.3%) men in TAX 327 eventually received 10 cycles and it also reflects more benign tumor biology [15]. In our study, except 1 of 15(6.7%) patient who developed progressive in disease in 8 cycles and was administered to radiotherapy, 12 of 15(80%) patients completed 10 cycles of chemotherapy.

Hematological adverse effects, especially febrile neutropenia and all grade neutropenia, is always a concern with chemotherapy especially imposing docetaxel. Analysis of docetaxel results in TAX 327[3] showed 90% of the patients reported at least one treatment emergent adverse effects, serious adverse effects were reported less commonly in individual patients. In the docetaxel arm, the incidence of grade 3-4 neutropenia was 32 %, and the febrile neutropenia was reported 3-6 %. Similarly, in the SWAG99-16, serious hematological adverse effects were rare, and the rate of grade 3-4 neutropenia was 16.1 % and the febrile neutropenia was reported 5 % [5]. However, in our study the grade 3-4 toxicity was not observed rather grade 2-3 toxicity was found with neutropenia in 26.6% of the patients and febrile neutropenia in 6.7 % patients.

The toxicities level that is seen in our study was comparable to TAX 327 trial. We believe the maximum similarities in the characteristics of patients between two studies such as age, pathological grading of prostate cancer, anemic conditions, alkaline phosphatase level and PSA level at the time of docetaxel imposed may have contributed the results. Our study has several limitations. First, this was non- randomized single institute based study; therefore, caution should be undertaken interpreting the conclusions. Second, the number of patients enrolled in the study was not sufficiently large, thereby decreasing the statistical power of results.

CONCLUSIONS
Docetaxel three weekly once with prednisone daily has been shown well tolerated with manageable adverse events in mandarin Chinese with CRPC men. However, the further randomized study in multicenter in large number of patients is required to evaluate the usefulness of the results.

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[1] Yao Zhu, Hong-Kai Wang, Yuan-Yuan Qu, Ding-Wei Ye Prostate cancer in East


