Preliminary efficacy and tolerability of chemohormonal therapy in metastatic hormone-naïve prostate cancer: The first real-life experience in Asia

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Abstract

Introduction: A substantial survival benefit with chemohormonal therapy has been proven by the CHAARTED and STAMPEDE studies, and this clinical approach has emerged as the standard of care for patients with metastatic hormone-naïve prostate cancer (mHSPC). However, because its clinical efficacy and tolerability in Asian patients remains uncertain, this study aims to evaluate preliminary results of its use in Hong Kong.

Methods: The clinical records of mHSPC patients treated with chemohormonal therapy from all six public oncology centers in Hong Kong between January 2015 and July 2016 were reviewed. Time to castration-resistant prostate cancer (CRPC), treatment-related complications, prostate-specific antigen (PSA) response and the time to PSA nadir were assessed.

Results: A total of 32 patients (median age, 66 years) were treated with chemohormonal therapy in the review period. After median follow-up time of 11.4 months, the median time to CRPC and time to PSA nadir were 19.5 months and 7 months, respectively. PSA response (>50% drop in PSA level from baseline) was achieved in all patients and the median maximal PSA response was 99.6%. The rates of grade 3 or 4 febrile neutropenia, neutropenia and anemia were 12.5%, 40.6% and 3.1%, respectively.

Conclusion: Early efficacy with chemohormonal therapy in Asian mHSPC patients was comparable to the pivotal study and biochemical response is promising. The high frequency of hematologic toxicities in Asian patients highlights the importance of proper patient selection and pre-emptive use of granulocyte colony-stimulating factor.

KEYWORDS
ADT, docetaxel, GCSF, prostate cancer

1 INTRODUCTION

Prostate cancer is the third most commonly diagnosed cancer among males in Hong Kong.1 The incidence rate reflects the largest increase recorded among the common male cancers over the past two decades. According to the latest figures released by the Hong Kong Cancer Registry, there were more than 1709 newly diagnosed cases, which accounted for 11.3% of all new male cancer cases, in 2014.2 The age-standardized rate of prostate cancer incidence also increased from 11.5 per 100 000 men in 1992 to 28.5 per 100 000 men in 2014.1 Despite the advancement of surgical techniques together with the increasing availability of different systemic therapies, trends in prostate cancer prevalence, incidence and survival suggest that the number of men with prostate cancer who require treatment will augment in the coming years.3,4 Therefore, new and promising treatment options are needed to effectively control the prostate cancer disease burden with minimal impact to the patients’ quality of life.
It has been well documented that prostate cancer can be influenced by androgenic activity in the body. In 1940, regression of metastatic prostate cancer was proven to be achievable by castration, either surgically or chemically. Since then, androgen deprivation therapy (ADT) has become the mainstay of first-line treatment for metastatic prostate cancer. Although the majority of the patients (>90%) initially respond to ADT, resistance occurs in most patients with a median survival of approximately 3 years, with patients ultimately progressing to castration resistance. Docetaxel in combination with prednisolone has been demonstrated to improve survival and quality of life in patients with metastatic castration-resistant prostate cancer (mCRPC). By demonstrating an extended survival benefit of 2.5 months, these results have changed the standard of care for mCRPC from mitoxantrone/prednisone to docetaxel/prednisone. However, the ideal regimen remains controversial, with continuing debates which include the optimal number of treatment cycles, and whether a fixed number of cycles should be given until the best response or intermittent treatment to avoid excessive toxicity. No standard second-line treatments emerged until 2010, in which other therapeutic options including sipuleucel-T, cabazitaxel, abiraterone acetate, enzalutamide and radium-223 began to show decent survival benefits.

In terms of clinical outcomes among the therapeutic interventions in the mCRPC setting, survival benefits are not robust, that is up to 5 months as demonstrated in most clinical trials. However, the recent publication of two randomized phase 3 trials that evaluated the combined use of ADT with docetaxel in men with metastatic hormone-sensitive prostate cancer yielded remarkable overall survival benefits of 13.6 months (CHAARTED) and 10 months (STAMPEDE) compared with ADT alone. The clinical benefit at this early analysis was more pronounced among patients with a higher burden of disease. The results demonstrated superiority in overall survival across all previous histologic mPC trials. Based on consistency of the data and the benefits provided, docetaxel in addition to ADT is recommended as the standard of care for men with newly diagnosed hormone-naive prostate cancer (mHSPC) in many international guidelines.

Currently, there have been no studies conducted in an Asian population for the concurrent use of ADT and docetaxel in the hormone-naive setting. We sought to evaluate the efficacy and toxicities of this combinational regimen in mHSPC patients with high-volume disease from all six public oncology centers in Hong Kong.

2 | METHODS

2.1 | Population of interest

2.1.1 | Ethics statement

The study was approved by the institutional review board of the authors’ institutions (Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee/Ref no.: CRE-2017.396). Permission to access the medical records through the inter-hospital computer network was granted by the aforementioned review board. The principles of the Helsinki Declaration were applied and followed. Permission to access the medical records was granted by the same board. Informed consent was obtained from patients before starting the treatment.

2.1.2 | Study population and treatment

The present study included patients with metastatic prostate cancer between January 2015 and July 2016, who had completed six cycles of combination chemotherapy with docetaxel and ADT in six Hong Kong public oncology centers (Prince of Wales Hospital, Queen Elizabeth Hospital, Pamela Youde Nethersole Eastern Hospital, Queen Mary Hospital, Tuen Mun Hospital and Princess Margaret Hospital). These patients received docetaxel in the upfront setting as an off-label drug, prior to approval. Chemotherapy was given to patients who remained castration-sensitive.

2.1.3 | Data collection and outcome measures

Electronic clinical records of the patient cohort were retrieved from the inter-hospital computer network. The definitions of clinical, biochemical and radiologic progressive disease were according to the Prostate Cancer Clinical Trials Working Group criteria. Tumors that were progressing with castrate levels of testosterone were classified as castration resistant according to the criteria. PSA levels were measured at each scheduled visit. Imaging (computed tomography [CT] of the abdomen and pelvis, technetium-99 m bone scanning and radiography or CT of the chest) was performed at baseline and at the time of documented castration resistance or as clinically indicated. Patients who had biochemical progression was defined as an increase in the PSA level of more than 50% above the nadir reached after the initiation of ADT, with two consecutive increases at least 2 weeks apart. The time to CRPC was defined as the time until documented clinical or serologic progression with a testosterone level of less than 50 ng per deciliter. The time to clinical progression was defined as the time until increasing symptoms of bone metastases; progression according to RECIST, version 1.0; or clinical deterioration due to cancer according to the investigator’s opinion. Treatment-related toxicities were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) 4.02 toxicity scale.

2.1.4 | Statistical analysis

Survival analyses were conducted using a Kaplan–Meier plot of CRPC-free survival. Adverse events (AEs) were recorded and graded according to the NCI CTCAE version 4.02. Any laboratory result anomaly fulfilling the criteria for a serious AE was also documented. All statistical analysis was carried out by the Statistical Package for the Social Sciences (Windows version 17.0.1.80; SPSS Inc., Chicago, IL, USA). The significance level was set at P < 0.05, and P values were given for two-sided testing.
Table 1: Baseline characteristics of the patients

| Characteristics                          | ADT plus Docetaxel (n = 32) |
|-----------------------------------------|-----------------------------|
| Age, years                              | 66                          |
| Range                                   | 53–74                       |
| ECOG score, number (%)                  | 7 (21.9%)                   |
| 0                                       | 24 (75.0%)                  |
| 1                                       | 1 (3.1%)                    |
| Co-morbidities, number (%)              |                             |
| Hypertension                            | 7 (21.9%)                   |
| Diabetes mellitus                       | 3 (9.4%)                    |
| Ischemic heart disease                  | 1 (3.1%)                    |
| Metastasis as initial presentationa, number (%) |               |
| Yes                                     | 31 (96.9%)                  |
| No                                      | 1 (3.1%)                    |
| Symptomatic at presentationb, number (%) | 9 (28.1%)                  |
| Gleason Score                           |                             |
| < 8                                     | 4 (12.5%)                   |
| 8–10                                    | 25 (83.3%)                  |
| Unknown                                 | 3 (9.4%)                    |
| Median baseline PSA, ng/mL (range)      |                             |
| Pre-ADT PSA                             | 285.2 (44.1–5491)           |
| Pre-chemo PSA                           | 46.6 (1.2–2091)             |
| Median baseline hemoglobin, g/dL (range)| 13.0 (9.6–14.4)             |
| Median baseline ALP, U/L (range)        | 207 (64–2949)               |
| Disease location, number (%)            |                             |
| Bone only                               | 24 (75.0%)                  |
| Lymph node                              | 7 (21.9%)                   |
| Lung                                    | 1 (3.1%)                    |
| Liver                                   | 0                           |
| Number of bone metastases, number (%)   |                             |
| Nilc                                    | 2 (6.3%)                    |
| < 4d                                    | 1 (3.1%)                    |
| 4–10                                    | 12 (37.5%)                  |
| > 10                                    | 14 (43.8%)                  |
| Superscan                               | 3 (9.4%)                    |

aPrevious treatment: Radical prostatectomy and refusal of salvage radiotherapy at progression.
bRequired WHO level II/III analgesics.
cWith lung/lymph node metastasis.
dLarge sacral metastasis.
ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; PSA, prostate specific antigen; ALP, alkaline phosphatase.

Table 2: Treatment details

| Characteristics                          | ADT plus Docetaxel (n = 32) |
|-----------------------------------------|-----------------------------|
| Median time from ADT to chemo, months (range) | 1.5 (0.03 – 6.23)          |
| Chemotherapy dose, number (%)           |                             |
| 75 mg/m2                                | 31 (96.9%)                  |
| 60 mg/m2                                | 1 (3.1%)                    |
| Chemotherapy Cycles, number (%)         |                             |
| < 6                                     | 2 (6.3%)                    |
| 6                                       | 27 (84.4%)                  |
| 7–10                                    | 3 (9.4%)                    |
| GCSF, number (%)                        |                             |
| Primary induction                       | 5 (15.6%)                   |
| Secondary induction                     | 6 (18.8%)                   |
| Chemo dose modification, number (%)     |                             |
| Due to hematologic toxicity             | 2 (6.3%)                    |
| Due to neuro-toxicity                   | 3 (9.4%)                    |
| Due to financial reasons                | 1 (3.1%)                    |
| Chemo schedule delay, number (%)        |                             |
| Due to hematologic toxicity             | 5 (15.6%)                   |
| Due to liver toxicity                   | 1 (3.1%)                    |
| Others                                  | 1 (3.1%)                    |
| Chemo Discontinuation reason            |                             |
| Completed ≥6 cycles                     | 30 (93.8%)                  |
| Toxicity                                | 1 (3.1%)                    |
| Disease progression                     | 1 (3.1%)                    |

ADT, androgen deprivation therapy; GCSF, granulocyte-colony stimulating factor.

3 RESULTS

3.1 Patient demographics

Thirty-two patients were included for the assessment during the study period and their baseline characteristics are shown in Table 1. The median age at the start of treatment was 66 (range, 53–74) years, which is comparable to the CHAARTED and STAMPEDE studies. The median time from ADT to chemotherapy was 1.5 months, and the median follow-up duration was 11.4 (3.9–26.6) months. The majority of the patients had a good performance status score (between 0 and 1) on the Eastern Cooperative Oncology Group scale. The local cases showed a higher disease burden compared to the CHAARTED and STAMPEDE studies, which was demonstrated by a median pre-ADT PSA level of 285.2 ng/mL (44.1–5491 ng/mL) compared to 56 ng/mL in CHAARTED and 70 ng/mL in STAMPEDE. Most (83.3%) patients had a Gleason score between 8 and 10 compared to 67.2% in CHAARTED and 74% in STAMPEDE. The disease location mainly occurred in bone or lymph node except for one patient who had lung metastasis. A majority of the patients (96.9%) had high volume disease (≥4 bone metastases or visceral metastases) as in CHAARTED study.

Table 2 shows the treatment details of the mHSPC patients, who received a 75 mg/m² dose of chemotherapy except for one who received a 60 mg/m² dose (elderly patient). Thirty patients (93.8%) completed six or more cycles of chemotherapy with docetaxel. Docetaxel was given every 3 weeks without prednisolone or steroid. One patient discontinued chemotherapy due to toxicity and one patient discontinued treatment due to disease progression. Seven patients had
The time to castration-resistance-free survival for metastatic hormone-sensitive prostate cancer patients treated with a chemohormonal regimen of docetaxel and androgen deprivation therapy [Colour figure can be viewed at wileyonlinelibrary.com]

### TABLE 3 Treatment-related complications among the 32 patients who received the chemohormonal regimen

| Event             | Grade 1–2 (%) | Grade 3–4 (%) |
|-------------------|--------------|--------------|
| Febrile neutropenia | 0            | 4 (12.5)     |
| Neutropenia        | 3 (9.4)      | 13 (40.6)    |
| Thrombocytopenia   | 0            | 0            |
| Anemia             | 19 (59.4)    | 1 (3.1)      |
| Neuropathy         | 13 (25.0)    | 0            |
| Fatigue            | 14 (43.8)    | 0            |
| Diarrhea           | 5 (15.6)     | 0            |
| Stomatitis         | 5 (15.6)     | 0            |

Delayed chemotherapy schedule, in which five of them due to hematologic toxicity and one due to liver toxicity. Primary granulocyte colony stimulating factor prophylaxis was administered to 11 patients at the discretion of the attending oncologist irrespective of the presence of any neutropenia sepsis.

### 3.2 Primary endpoint – Time to CRPC

After a median follow-up of 11.4 months, the median time to castration-resistance was 19.5 months (Figure 1), which is comparable to the result found in the CHAARTED study (i.e. 20.2 months).

### 3.3 Secondary endpoints – prostate-specific antigen (PSA) response, time to PSA nadir and treatment-related complications

The median time to PSA nadir was 7 months. The PSA response (>50% drop in PSA level from baseline) was achieved in all patients, and the median maximal PSA response was 99.6%.

Table 3 shows the treatment-related complications among the mHSPC patients who received the chemohormonal regimen. The rates of grade 3 or 4 febrile neutropenia, neutropenia and anemia were 12.5%, 40.6% and 3.1%, respectively, while no cases of grade 3 or 4 thrombocytopenia, neuropathy, fatigue, diarrhea or stomatitis were reported.

### 4 DISCUSSION

The current study reported the use of ADT and docetaxel in the Asian population in the hormone-naive setting. The current cohort demonstrates that chemohormonal therapy has good efficacy in Chinese mHSPC patients, while chemotherapy-related hematologic toxicities were observed in Chinese patients which suggests the need to have proper patient selection.

ADT has been recognized as the standard treatment for mHSPC, while recent clinical trials such as CHAARTED and STAMPEDE have shown that ADT in combination with chemotherapy could result in greater survival benefits compared with ADT alone. In CHAARTED, upfront docetaxel with ADT improved overall survival from 44 months with ADT alone to 57.6 months (hazard ratio [HR] 0.61; 95% confidence interval [CI], 0.47–0.8; \( P < 0.0001 \)). In addition, in the sub-group with high volume disease, the benefit was more apparent (49.2 months vs 32.2 months; HR 0.60; 95% CI, 0.45–0.81; \( P < 0.0001 \)). In STAMPEDE, consistent benefits were observed. Median overall survival was improved from 71 months for standard of care only to 81 months for chemohormonal therapy (HR 0.78; 95% CI 0.66–0.93; \( P = 0.006 \)). The additional survival benefit of combination therapy was also demonstrated in a meta-analysis, which found a 9% absolute improvement in survival at 4 years with ADT plus docetaxel compared to ADT alone among mHSPC patients. These results form the basis for the recommendation of combined ADT and chemotherapy as the new standard for mHSPC in several international guidelines, which include the European Society for Medical Oncology, the National Comprehensive Cancer Network and the European Association of Urology.

Here, the efficacy and complications of the combined treatment of ADT and docetaxel in Chinese mHSPC patients are reported for the first time. The inclusion of mHSPC patients from all Hong Kong public oncology centers during a defined period provides a representative sampling of the efficacy of combined ADT and docetaxel therapy in a clinical setting. The early primary time point, which is represented by the median time to castration resistance, was comparable to the pivotal trial, the CHAARTED study (19.5 vs 20.2 months), even though patients with a higher disease burden were included in this study (high volume patients 96.9% in current study vs 66.2% in CHAARTED). All patients achieved a significant PSA response, which is represented by a >50% reduction in PSA level from baseline, and the median maximal PSA response was 99.6%. The median time to achieve PSA nadir was 7 months. These results suggest that ADT plus chemotherapy has similar efficacy in Chinese mHSPC patients and the Western patient populations. Other clinical parameters such as mortality and survival data mandates longer follow-up to determine if the local cases will have further improvements in survival rate compared to the CHAARTED or STAMPEDE studies.
CONCLUSION

Most (93.8%) of the patients completed six or more cycles of docetaxel and 96.9% of patients had no dose reduction (Table 2). In our cohort, the patients did not receive prednisone or any other steroid with chemotherapy, similarly as the CHAARTED study. Compared with previous reports, grade 3 or above hematologic toxicities such as neutropenia, febrile neutropenia and anemia were more frequent in Chinese patients in the current study compared with Western populations (Table 4). While there were reports of neuropathy, fatigue, diarrhea and stomatitis among the Caucasian patients in the CHAARTED and STAMPEDE studies, there were no reports of these toxicities in the current study. The incidence rates of the various hematologic toxicities also resemble our previous study cohort, demonstrating that the toxicity profile is consistent among Chinese patients. Pre-emptive use of granulocyte-colony stimulating factor (GCSF) to alleviate hematologic toxicity is suggested in these patients when docetaxel combination therapy is adopted. According to local clinical experience, docetaxel had been given to elderly patients of up to 80 years of age. Therefore, age may not necessarily be a critical factor in deciding whether to initiate the chemohormonal treatment. Instead, other factors, such as patient's general health conditions and presence of comorbidities, are to be considered.

We observed differences in clinical practice, selection bias and data collection between hospitals, which is typical of real-world practice. The inconsistent treatment protocols and policies between hospitals during data collection adds a further drawback to this study; therefore, a consensus is necessary to draw consistent treatment guidelines. Further follow up is needed to accurately define progression-free survival and overall survival.

| Event          | Current study (%) | Poon et al22 (%) | CHAARTED14 (%) | STAMPEDE15 (%) |
|---------------|------------------|-----------------|--------------|---------------|
| Febrile neutropenia | 12.5             | 14.1            | 6.1          | 15            |
| Neutropenia    | 40.6             | 47.4            | 12.1         | 12            |
| Thrombocytopenia | 0                | 0               | 0.3          | 0             |
| Anemia         | 3.1              | 10.6            | 1.3          | 0             |
| Neuropathy     | 0                | 0               | 0.5          | 3             |
| Fatigue        | 0                | 0               | 4.1          | 7             |
| Diarrhea       | 0                | 1.8             | 1.0          | 8             |
| Stomatitis     | 0                | 1.8             | 0.5          | 0             |

*a57 metastatic hormone-sensitive prostate cancer Chinese patients treated with docetaxel.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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