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Advanced Prostate Cancer Management: Proceedings of a scientific session, 20-21 July 2018, Manila, Philippines

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CONFERENCE REPORT

Abstract

Prostate cancer, the second most common cancer worldwide in 2012, poses a high public burden prompting the need to develop effective treatment strategies. To determine the progress made through the years, this paper documented the timeline of treatment strategies for advanced prostate cancer as presented in a scientific session held in July 2018. Two treatment strategies for metastatic prostate cancer were emphasized: the addition of docetaxel (chemotherapy) and abiraterone acetate plus prednisone to androgen-deprivation therapy (i.e. standard of care). Related clinical trials including but not limited to the CHAARTED trial, STAMPEDE trial, and LATITUDE trial showed that addition of either DOC or ABI led to a general increase in the overall survival of the patient. Furthermore, treatment strategies for non-metastatic castration resistant prostate cancer were also discussed. Evidence from clinical trials showed that addition of enzalutamide or apalutamide to ADT yielded better outcomes than ADT-placebo. These recent advancements have broadened the physician's options for treatment.

Introduction

In men, prostate cancer was the second most common cancer with 952,000 cases corresponding to 6.8% of the total worldwide in 2012 [1]. It is also the fifth most common cause of death from cancer [1]. In Filipino men, it is the third and fourth leading cancer in terms of new cases and new deaths, respectively, in 2015 [2]. Furthermore, a study by Wong et al (2016) identified the Philippines as one of the three countries experiencing a substantial increase in both incidence and mortality rates [3].

The high public health burden associated with prostate cancer prompts the need to develop effective treatment strategies. Several developments have been made starting from the discovery of hormone treatment by Charles Huggins in the 1940s until the recent advancements in drug discovery. In 2014, the Food and Drug Administration approved five newly developed drugs such as sipuleucel-T, radium-223, abiraterone, enzalutamide, and cabazitaxel [4].

To determine the progress made through the years, this paper documented the timeline of treatment strategies for advanced prostate cancer as presented in a scientific session.

The Scientific Session

A scientific session titled "The Oncology Urology Roadshow" was presented by Dr. Kurt Miller, professor of urology and Department Chair at the Benjamin Franklin Medical Center in Berlin, Germany, on 20-21 July 2018 in Mandaluyong City, Philippines. The first day of the event was held for medical oncologists while the second day was for urologists. A separate session for the two specialists was done to encourage discussion and best-practice sharing.

For both days, the session started with Prof. Miller's discussion on the different treatment and management strategies for advanced prostate cancer, followed by an open forum. At the end of the session, one of the organizers summarized the major points to be validated by the speaker and the participants.

The documentors (CHT, AHT) prepared a transcription of the session using their audio-recordings and field notes of the event. The transcription was used to obtain the major discussion points of the lecture.

This paper provided a documentation of a scientific session, and was supported by Johnson & Johnson (Philippines), Inc. The funder did not have any direct role in the analysis and interpretation of data derived from the discussion.

Table 1. *Distribution of physicians who attended the forum, by specialty and area of practice*

	Private	Public	Total
Oncologist	7	5	12
Urologist	12	18	30
General Practioners	1	0	1
Total	20	23	43

A total of 43 physicians attended the scientific session. 12 medical oncologists participated in the first day while 30 urologists and one general practitioner participated in the second day. Table 1 shows the profile of the participants.

The Critical First in Advanced Prostate Cancer Management

The discussion started with a general timeline of researches and clinical trials on treatment strategies of advanced prostate cancer. In 1941, the Androgen Deprivation Therapy (ADT) or hormone therapy was introduced. In ADT, the level of androgen in the male's body is reduced through orchiectomy or castration, complete androgen blockade (CAB), and the like. Cure in at least 90% of cases after giving CAB alone for 6.5 years was observed in a study by Labrie (2005) [5]. This suggests that a combination of a GnRH agonist and a pure anti-androgen could possibly be the most efficient treatment regimen for localized prostate cancer that can also eliminate the possibility of death [5]. To further prove this point, a meta-analysis from the Prostate Cancer Trialists' Collaborative Group done in 2000 was presented where a survival advantage of 2.9% was observed in patients treated with ADT plus nilutamide or flutamide (i.e. anti-androgen) compared with ADT alone [6].

The discussion moved forward to the different recommendations for the first-line treatment of metastatic disease. Two recommendations that received a "strong" rating were emphasized: (1) the castration plus docetaxel (chemotherapy) and (2) the castration plus abiraterone acetate plus prednisone. These two strategies had been the focus of the lecture [7].

A series of clinical trials involving the two treatment strategies were tackled. First was the study "Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomized, open-label, phase 3 trial" by Gravis et al (2013) [8]. A median overall survival (OS) of 58.9 months was observed in the group given ADT plus docetaxel (DOC) in contrast with the 54.2 months in the group given ADT alone [8]. However, the findings were considered insignificant due to the small number of participants.

The second study presented was the 2015 "Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer" (CHAARTED) by Sweeney *et al*[9]. This had a similar design with the GETUG study but was originally designed for high volume disease (HVD). A higher median OS of 57.6 months was observed in the group treated with ADT plus DOC compared with the 44.0 months in the group treated with ADT alone—a difference of more than one year [9]. This positive finding was unexpected and unheard of in oncology during that time.

The CHAARTED study also explored the applicability of ADT-DOC in various cases. A comparison between de novo HVD and prior local treatment HVD was done. In both cases, a higher median OS was observed in the group treated with ADT-DOC, with higher median OS in the prior local treatment HVD arm [9]. Meanwhile, comparison by disease burden yielded a different result. A higher median OS was observed in HVD patients treated with ADT-DOC but low volume disease (LVD) patients treated with ADT alone had a higher median OS than those with ADT-DOC [9]. However, results were all based on bone and imaging scans. This significant finding implies that chemohormonal therapy may not work for everyone.

The third study, the STAMPEDE trial by James et al, was divided into two. The first trial involved the addition of DOC and/or zoledronic acid (ZA) to the standard of care (i.e. ADT). Men included in this trial had a high-risk locally advanced or metastatic prostate cancer starting long-term hormone therapy for the first time [10]. Patients treated

with ADT plus DOC had a median OS of 65 months while those treated with ADT alone had a median OS of 43 months [10]. The difference of 22 months was even more impressive, hence considered as a significant overall advantage. On the other hand, a higher percentage of adverse events (e.g. febrile neutropenia) was observed in groups treated with ADT-DOC and ADT-ZA-DOC than ADT and ADT-ZA [10].

The second trial was in 2017 involving the addition of abiraterone acetate (ABI) to ADT for high-risk advanced prostate cancer. A 37% and 71% improvement in overall survival and failure-free survival (i.e. time to failure), respectively, was observed upon adding ABI [11]. Moreover, no good evidence of heterogeneity by metastatic status had been found [11]. In terms of safety, the ADT and ADT-ABI group had similar number of adverse events except in cardiovascular disorders and gastrointestinal disorders (particularly hepatic disorders) where the latter had a higher percentage of events [11].

The last among the studies on metastatic prostate cancer discussed was the LATITUDE trial by Fizazi *et al* [12]. This study enrolled newly diagnosed patients with high-risk metastatic hormone-naïve prostate cancer to compared two interventions: ADT plus ABI plus prednisone versus ADT plus placebo. The OS rate at three years of the ADT-ABI-P group was 66% while that of the ADT-placebo was 49%. A statistically significant 38% risk reduction of death was associated with the ADT-ABI-P group [12]. A statistically significant improvement was also achieved in all secondary endpoints such as time to Prostate-Specific Antigen (PSA) progression, time to pain progression, time to next symptomatic skeletal event, time to chemotherapy, and time to subsequent prostate cancer therapy [12]. On the other hand, a higher percentage of adverse events including hypertension, hypokalemia, increase in ALT and AST, and cardiac disorders was seen in the ADT-ABI-P group [12].

After discussing all these studies, DOC and ABI were compared. Adding either of the two to ADT led to better outcomes as proven by the various trials conducted. Sydes et al then did a randomized analysis of data from the STAMPEDE trial to compare the two treatment strategies [13]. No significant evidence of difference was found in the overall and prostate cancer-specific survival and symptomatic skeletal events [13].

On the other hand, Tan et al (2018) did a meta-analysis of seven trials including the ones discussed earlier where they also differentiated the two treatment strategies along with others [14]. They found that ADT-ABI is superior to ADT-DOC in terms of overall survival and failure-free survival, even deducing that the former could possibly exceed the addition of DOC, bisphosphonates, celecoxib, or combinations in the same parameters [14]. Moreover, adding ABI reduces the risk of death by 19% compared with adding DOC. The two can then be said to differ with regards to safety [14].

After an extensive discussion of metastatic prostate cancer, discussion proceeded with non-metastatic castration-resistant prostate cancer (nmCRPC). There is currently no approved treatment strategy for nmCRPC. For these patients, one of the most important but unmet goals is preventing metastasis since it is a major contributor to morbidity and mortality [15].

Different studies were again cited to tackle the topic. First off was the PROSPER study, a randomized placebo-controlled trial of enzalutamide in men with nmCRPC, by Hussain et al (2018) [16]. The primary endpoint of this study is the metastasis-free survival (MFS), defined as the time from randomization until radiographic progression or death within 112 days of treatment discontinuation. The median MFS of the ADT-enzalutamide and ADT-placebo arms are 36.6 months and 14.7 months, respectively [16]. This 22-month difference is equivalent to a 71% reduction in relative risk of radiographic progression or death in the enzalutamide arm. A median time to PSA progression of 37.2 months was also observed in the enzalutamide arm in contrast with the 3.9 months in the placebo arm [16]. Overall, a 20% reduction in the relative risk of death was observed in the enzalutamide arm [16].

The second study presented was the SPARTAN trial wherein apalutamide was compared with placebo in nmCRPC patients [17]. The study design is similar with the PROSPER study, except that this utilizes a different drug. The median MFS of the ADT-apalutamide arm was 40.5 months while that of the ADT-placebo arm was 16.2 months, resulting to a 72% risk reduction of distant progression or death [17]. A 94% risk reduction of PSA progression in the apalutamide arm and an overall 30% risk reduction of death were observed [17]. However, more adverse events such as fatigue, rash, and weight loss, among others, were seen in the apalutamide arm [17].

Open forum for medical oncologists

A total of six questions were raised by medical oncologists during the open forum. The first one was a clarification on the difference between the metastatic

hormone-sensitive prostate cancer (mHSPC) and metastatic castration-resistant prostate cancer (mCRPC). According to Prof. Miller, the two are easy to differentiate because nobody is born with castration resistance. Therefore, all newly diagnosed patients are always hormone-sensitive. DOC and ABI are also used for newly diagnosed patients; hence both can be immediately indicated for patients who reached the metastatic phase.

The second clarification was regarding the results of the study by Sydes *et al* [13] comparing DOC and ABI as demonstrated in a forest plot. Prof. Miller explained that when the result of the study (shown as a point) crosses the vertical line at the middle, then no statistically significant difference has been observed between the two comparators. That is why Sydes et al concluded that there is no significant difference between DOC and ABI [13]. He also mentioned that "…the most striking argument is probably the side effect profile of DOC versus ABI." In daily practice, most patients are given ABI rather than DOC due to this. He also mentioned that there is an ongoing research on the effect of ADT plus DOC plus ABI.

The third clarification was on the definition of high volume disease. In one study, HVD was defined as having four or more metastases and metastasis outside the pelvis. Prof. Miller responded that this is just an "artificial" definition of HVD. Regardless of whether the patient has high volume or low volume disease, the fact that he has metastatic prostate cancer means he will die from it unless he has a high risk for cardiovascular disease or untreated myocardial infarction. For Prof. Miller, all these patients need to be given either DOC or ABI to help them survive in real life. He said that "…I have never seen a patient to whom I cannot give ABI except when he/she has high liver enzymes" and that "…DOC has many side effects, but it can still be given to many patients." If a patient comes with a metastatic disease, he would definitely treat him using either of the combinations.

Question 4 was about the sequencing of the treatment strategies. The participant mentioned that DOC is usually given when the patient is still fit while ABI is used when the patient is not as healthy when he/she is first diagnosed. According to Prof. Miller, there is no evidence that giving DOC before ABI or vice-versa is better than the other. Therefore, he finds taking the route with fewer side effects as more appealing for the patient. If for an instance, a patient with mHSPC is treated using ADT-ABI but after a while, gets PSA progression. In this case, enzalutamide or DOC can be given since the response rates following ABI for both are 31% and 40%, correspondingly.

The fifth question was on the validity of MFS as the endpoint in the trials on nmCRPC instead of the overall survival. To this, Prof. Miller responded that MFS is a patient-relevant endpoint. Since metastasis is associated with severe morbidity, avoiding it will improve the quality of life of the patient. From a clinician's point of view, avoiding it is good news.

Lastly, one participant asked about the validity of AR-V7 as a predictive marker. Prof. Miller said that AR-V7 was meant to be a negative predictive factor. Hence, the presence of the marker means that the treatment is not effective.

Open forum for urologists

The participants raised seven questions for Prof. Miller. The first question was about recommending ADT-ABI to patients with newly diagnosed metastatic prostate cancer with low volume metastasis. He said that he would be very comfortable to recommend this combination because many trials (e.g. LATITUDE) could back up this decision. He also thought that the risk of making a mistake here is low.

The next question was whether there is a high population of patients in Germany who can receive DOC. According to Prof. Miller, there are no real figures of this in Germany. There is also no definite characterization of a "candidate patient" for this treatment yet. Moreover, he was asked whether there have been studies comparing LH-RH agonists and orchiectomies. For him, difference between the two does not matter because both have the same effect of reducing the level of testosterone in the body.

The fourth question was on recommending the start of ABI to patients who are currently doing well under ADT alone. He claimed that there is no evidence yet that can prove that administering ABI early is better for the patients. However, if the metastatic phase comes in early, then ABI can be given. The clinician should also not wait for PSA progression before starting ABI. One participant also added that the Food and Drug Administration is about to approve the ABI therapy. Therefore, if the patient has been diagnosed with metastatic prostate cancer, he/she can already start with ABI.

The fifth question was on the importance of differentiating between hormone-sensitive and castration-resistant prostate cancer as well as HVD and LVD. Similar with his answer during the first Q&A, Prof. Miller reiterated that classifying the disease as high volume or low volume is no longer necessary because metastatic prostate cancer is already lethal in itself. He also said that the difference between HSPC and CRPC lies on the time of presentation. All cases of prostate cancer first show up as HSPC while CRPC presents itself as the disease progresses.

Q6 involved the possible adverse events brought by prednisone (5 mg). Prof. Miller thought it would not be a problem since there is no cumulative toxicity, hypercalcemia, problems in bone density, and other problems associated with prednisone observed in studies. However, he was not sure what the basis of the restriction to 5 mg was.

The last question was on the role of co-morbidities in choosing the therapy for a patient. To this, he answered that co-morbidities may be used to choose one treatment over another, but this rarely happens unless for example, there are elevated liver enzymes, in which case the use of ABI would not be an option. In more common cases such as diabetes for instance, what is usually done is to control it and continue with the treatment for the prostate cancer.

Discussion

In most cases, prostate cancer only becomes life-threatening when it has already spread to other sites such as the bones and lymphatic nodes, a condition known as metastatic prostate cancer (Philippine Cancer Society). This paper discussed three main treatment regimens for metastatic prostate cancer: hormone therapy, chemotherapy and anti-cancer drugs.

Hormone therapy, also known as androgen-deprivation therapy, deals with reducing the production of male hormones that the cancer cells use to grow and develop. Charles Huggins' discovery of this treatment marked a “new era in prostate cancer therapy” [18]. In the trials mentioned in this paper, hormone therapy was the constant variable present in the groups compared being the standard of care. It is considered the most useful [18] and the first-line of treatment against advanced prostate cancer [19] for many years.

Chemotherapy, in the form of Docetaxel, has also been used to treat prostate cancer. The trials presented in this paper showed that adding DOC to the SOC generally increased the survival of patients. The significant findings of the CHAARTED and STAMPEDE trials established a new treatment standard for advanced prostate cancer [20]. It is also important to note that the CHAARTED trial found that there are more adverse events when DOC was added. Thus, in terms of safety, addition of DOC may not suit the patient very well. It still depends on the willingness of the patient and the physician to take the risk.

Lastly, abiraterone acetate, along with prednisone, was also found to be effective in improving survival from advanced prostate cancer. The findings of Tan et al (2018) [14] that ABI is superior to DOC both in terms of survival and safety could possibly establish another gold standard for treatment. Due to the good outcomes of ABI, its development has been considered a breakthrough in treating mCRPC [21].

The treatment for advanced prostate cancer has significantly improved over the years. The discovery of new strategies has broadened the physician's options for treatment. But like in any other disease, resistance to therapy can be developed. Thus, one of the challenges of the present time is to explore mechanisms of treatment resistance and develop ways to prevent it from happening.
On the other hand, treatment strategies for nmCRPC were also discussed. Trials showed that metastasis-free survival for both enzalutamide and apalutamide arms were better than for the placebo arm. This gives patients hope for prevention of progression to mCRPC. In the clinical setting, physicians can focus on confining the disease to the prostate if cure seems impossible.

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