Highlights of the 1st St Gallen Advanced Prostate Cancer Consensus Conference (APCCC), 12–14 March 2015

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Abstract

Over the past five years we have been experiencing a formidable advancement in advanced prostate cancer therapeutics. Notwithstanding the availability of a multitude of new agents to treat the disease, there are treatment decisions where there is either limited or conflicting evidence to guide us. Thus, an international expert consensus meeting was launched in an effort to provide expert recommendations as the basis for discussion with patients and help navigate some of the as yet, ‘uncharted waters’ of disease management.

Keywords: advanced prostate cancer, castration-resistant prostate cancer, hormone sensitive prostate cancer
Methods

It helps a lot to have a successful model on which to base a design, and in our case it was the St Gallen Breast Cancer consensus meeting. The ten most important areas of unmet need in advanced prostate cancer management were initially identified by the scientific committee. The panel included 41 members from 16 countries, covering different specialties (Figure 1). Questions based on the ten fields of interest were compiled employing a modified Delphi process and sent to panel for input. The questions were sent three times for review (Hsu C, Pract Assess Res Eval 2007;12:1–8). These were the ones voted for publicly on the last day of the conference.

Our recommendations apply only to non-frail patients and patients with adenocarcinoma of the prostate (if not stated otherwise). Cost was not a consideration for this consensus meeting.

Those of us lacking experience or with conflict had the option to opt for ‘unqualified to answer’ or ‘abstain’ respectively.

Ten most important topics in the management of advanced prostate cancer

1. Castration-naive metastatic prostate cancer management
2. Definition of castration resistance
3. Non metastatic (M0) Castration Resistant Prostate Cancer (CRPC) management
4. Use of endocrine manipulations without proven survival benefit in metastatic CRPC
5. Treatment sequencing for metastatic CRPC
6. Staging and treatment monitoring for advanced prostate cancer
7. Use of osteoclast-targeted agents for skeletal-related events (SRE) and symptomatic skeletal-related events (SSE) prevention in advanced prostate cancer
8. Value and use of predictive markers
9. Oligometastatic castration-naive prostate cancer
10. Management of patients
On the first two days of the meeting an outstanding series of lectures covering these topics and providing a glimpse into the future took place with a lot of interaction with the audience. With regard to the future we even got some breaking news presentations. One for instance, which particularly impressed me, was presented by Dr Arul Chinnayan concerning the molecular characterisation of prostate cancer.

The meeting was extremely well attended having reached capacity and even using the overflow space. Owing to this amazing response and enthusiasm, next time more than likely we will have to employ a larger conference centre similar to that used by the breast cancer meeting.

On the third day we spent all morning going over and discussing the 100 consensus questions which were put forth. In some we did reach a consensus. The ones in which we did not mainly reflect areas of unmet need and in my opinion would provide a good source of research questions.

I will try to briefly summarise our answers, whether we reached a consensus or not, and also include some background information.

1. Management of castration-naive metastatic prostate cancer

A. Androgen deprivation (consensus)

The panel (71%) would not provide intermittent ADT instead of continuous ADT to de novo metastatic castration sensitive prostate cancer with the exception of a minority of select patients. They would instead of continuous ADT.

This consensus is based on the (Southwest Oncology Group) SWOG 9346 trial, a hallmark study with >1500 patients with castration-naive metastatic prostate cancer randomised to intermittent versus continuous Androgen Deprivation Therapy (ADT). Results failed to prove non-inferiority of the intermittent ADT (Hussain m, NEJM 2013).

The panel would not suggest combined androgen blockade in the majority of patients.

Per meta-analyses of trial the overall survival (OS) advantage of combined ADT with antiandrogens versus ADT is modest (prostate cancer collaborative group Lancet 2000; Samson DJ Cancer 2002).

Data of combination with novel endocrine agents are not available as studies are ongoing.

B. Chemotherapy considerations (non-consensus)

Half the panel recommends docetaxel in the majority of M1 patients with high-volume disease, while 39% in a minority, and the rest do not. In patients with low volume disease chemotherapy is not recommended.

Two randomised phase III trials have tested the addition of docetaxel in the treatment of metastatic castration sensitive prostate cancer. GETUG-15 (n = 385) reported no survival benefit (Gravis G Lancet Oncol 2013). However the CHAARTED trial (SWOG 9346) (n = 790) reported at the American Society of Clinical Oncology (ASCO) 2014 —and not in a journal yet—has exhibited an outstanding clinical and of course statistically significant improvement exceeding a year of difference. This trial initially included only patients with high volume disease defined as presence of visceral metastases and/or ≥ four bone metastases (at least one beyond pelvis and vertebral column was required). However because of slow accrual the trial was later amended to also include low volume disease patients.

Potential explanations for the different OS result between the trials may be because of sample size, lower percentage of high volume patients in GETUG-15, and use of subsequent life-prolonging treatments (including docetaxel) and geographic screening differences leading to more aggressive phenotype identification in the metastatic setting in the USA, i.e. cancer that ‘escape’ screening only through rapid progression. The panel (61%) recommended the high-volume definition as used in CHAARTED.
C. Osteoclast-targeted therapy (consensus)

Per the panel, bone metastatic castration-naïve PCa should not be treated with either zoledronic acid (81%) nor denosumab (79%) at a dosing frequency for SRE-prevention.

There is a negative trial (CALGB90202) for zoledronic acid in this setting and no data on denosumab. We acknowledge that these agents (at lower dose/schedule) have without a doubt a role in the treatment/prevention of osteoporosis.

2. Definition of castration-resistance (consensus)

Per the panel (94%) testosterone levels should be monitored for a desired threshold of <50ng/dL (<1.7nmol/L) (per 82%) as a requirement for castration-resistance definition in the case of a rising PSA. A confirmed rising PSA with suppressed testosterone is thus considered sufficient for the characterisation of castration-resistance (per 94%). The addition of an antiandrogen and a withdrawal period are not warranted.

3. Castration-resistant prostate cancer non metastatic disease (M0 CRPC) (consensus in definition, imaging and treatment)

The panel recommends (91%) imaging in asymptomatic patients with rising PSA and/or rapid PSA kinetics on ADT and no metastases.

With regards to the total PSA cut-off to initiate imaging, the entire panel recommended a PSA below 20 as cut-off. [between a PSA of between 2 and 10 (54%) and a PSA between 10 and 20 (46%)]. For PSA-DT as a trigger for imaging, the panel recommends a PSA-DT of ≤ six months (74%). The panel (77%) consider negative Computed Tomography and bone scintigraphy as sufficient for diagnosis of M0 CRPC in clinical practice.

A rising PSA on ADT with no metastatic disease on imaging is largely dependent on the imaging used. M0 CRPC is likely artificial disease stage and a result of limited technology imaging advancement given that micrometastases are invariably present.

There was not a consensus regarding the need for treatment in this disease stage however the panellists acknowledge that a patient who knows that his PSA is rising on ADT is invariably stressed and is expectant of assistance.

Thus the panel (84%) support endocrine treatment without proven survival benefit in M0CRPC though when available a clinical trial is preferable.

4. Endocrine treatment without survival advantage in metastatic CRPC (consensus)

These include first generation antiandrogens, oestrogens, estramustine, ketoconazole, and corticosteroids (dexamethasone and prednisone/prednisolone). None of these confers survival advantage however some extent of biochemical and/or clinical regression may occur.

They are inexpensive and as far as low dose corticosteroids and antiandrogens are concerned relatively safe.

The panel members supported given availability of abiraterone and enzalutamide, that these ‘vintage’ agents are not appropriate treatments. However, in the case of non-availability one could consider them especially if chemotherapy is not an option either. Importantly, prescribing these new agents may occasionally be a concern even in countries with approval as reimbursement may only be partial and co-pay may be too high (especially in the United States).

The preferred first treatment option amongst these vintage agents is a first generation antiandrogen (63%), or dexamethasone (25%).
5. Treatment sequencing for metastatic CRPC (limited degree of consensus with areas of non-consensus)

With six treatment choices having shown prolongation of survival in metastatic CRPC, we are experiencing unprecedented times in the treatment of prostate cancer. However, there are no prospective data on sequencing choice and prioritisation. Hence decisions can be stressful, and is a significant concern for patients and physicians. Abiraterone and enzalutamide have exhibited OS in four large phase III trials pre- and post-docetaxel (de Bono NEJM 2011, Scher NEJM 2012, Beer NEJM 2014, Ryan NEJM 2013). Essentially four large trials are aligned in support of benefit with enhanced androgen signalling inhibition. Sipuleucel-T an immunotherapy was mainly tested in chemotherapy-naïve CRPC patients (Kantoff NEJM 2010). Cabazitaxel was only tested in patients progressing following docetaxel (de Bono Lancet 2010). Radium-223 phase III experience included post-docetaxel patients (57%) or patients unfit for or not wishing chemotherapy (Parker NEJM 2013).

The majority of the panel (63%) proposed starting treatment upon confirmation of progression even by PSA only. The remainder supported deferring given adequate disease monitoring.

The panel (71%) agreed that ‘no pain medication or only when needed (p.r.n.) pain medication’ is a meaningful definition of asymptomatic/mildly symptomatic (related metastatic CRPC patients though fatigue is an important consideration as well).

A. Novel androgen signalling inhibitors (Partial consensus on use, non-consensus on choice)

The panel (88%) supports abiraterone acetate or enzalutamide as first-line therapy for asymptomatic or minimally symptomatic CRPC patients in addition to ADT. Regardless of inclusion criteria in chemo-naive trials (i.e. non-inclusive of symptomatic patients), the panel (77%) felt only certain symptomatic patients could receive these agents as first line, though in my opinion that is very vague. Possible scenarios could include symptomatic patients refusing chemo or having non-disease related comorbidities. In a similar fashion the panel (88%) felt that it was appropriate to extrapolate the results of COU-302 to certain chemotherapy-naive patients with visceral metastases.

With regard to the preferred first-line endocrine agent, the panel did not reach a consensus and was divided between enzalutamide (39%), abiraterone (27%), or either one of the two (33%). Considerations for specific patient factors, concomitant medication and comorbidities, and patient’s preference concerning the expected side effects are essential when making a choice for either of the endocrine agents.

Based on the available, albeit retrospective, data indicating lack of activity of the endocrine agents when used sequentially the panel did not recommend (55%) or recommended only in a minority of selected patients (42%) second-line treatment with abiraterone acetate or enzalutamide, in otherwise healthy patients judged to have primary (innate) resistant disease (no PSA decline, no radiological improvement, no clinical benefit) to first-line abiraterone or enzalutamide.

In case of acquired resistance (initial response followed by progression) to first-line abiraterone or enzalutamide, 24% of the panel did not recommend and 53% recommended only in a minority of selected patients the other endocrine agent as immediate next line treatment.

B. Docetaxel (non-consensus)

The panel does not (49%) recommend docetaxel chemotherapy as first-line therapy for otherwise healthy asymptomatic/minimally symptomatic CRPC patients or does so only in a minority of selected patients (42%). In symptomatic patients the panel was divided with 41% recommending docetaxel as first-line treatment in the majority and 50% in a minority of selected patients.

Upon short-time (≤12 months) to CRPC (57%) half the panel recommend docetaxel in the majority of patients with symptoms.
C. Radium-223 (non-consensus)

The panel supports use of radium-223 in a minority of CRPC patients (55%) as first line. We must consider that ALSYMPCA trial was quite mixed in patients.

D. Sipuleucel-T (non-consensus)

The panel did not reach a consensus with regards to sipuleucel-T use in first-line therapy for asymptomatic CRPC patients without visceral metastases but agreed they would not use for patients with symptoms and/or visceral metastases.

E. Cabazitaxel (consensus for third line)

The panel reached a consensus for use of cabazitaxel as third line but not as second line.

6. Staging and treatment monitoring (extensive degree of consensus)

Most current guidelines do not provide clear recommendations—National Comprehensive Cancer Network (NCCN), European Association of Urology (EAU), European Society of Medical Oncology (ESMO)—for imaging. The prostate cancer working group II (PCWG2) recommendations provide only for patients in phase II clinical trials (Scher JCO 2008).

A. Pretreatment

The panel (100%) recommends pretreatment staging in metastatic CRPC patients to include history and clinical examinations [blood tests including hemoglobin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH)].

And imaging inclusive of a computed tomography scan of thorax and abdomen–pelvis (94%) and bone scintigraphy (92%) should be done pretreatment. Novel imaging technologies though attractive are still under evaluation per the panel.

Malignant spinal cord compression (MSCC) is one of the greatest ‘fears’ we face in the treatment of this disease. An magnetic resonance imaging (MRI) of the whole spine has to be done immediately when a cord compression is suspected.

B. On treatment follow-up

The panel (83%) did have a consensus, that regular image monitoring apart from clinical and laboratory assessment is warranted. This reflects the fact that the survival prolonging agents all have potential toxicity and considerable costs and patients with no objective benefit (including disease stabilisation) should not be exposed to these treatments.

PSA interpretation should be done with caution particularly at treatment initiation given a possible PSA flare phenomenon described mainly with chemotherapy treatment. Consulting and informing the patient about interpretation of PSA values is integral to treatment choices.

When treating with abiraterone or enzalutamide, the panel recommended PSA monitoring, (62%) every two to four months months and 38% recommended every three to fourweeks. The panel recommended regular CT scans with a frequency of every two to four months (47%) or every six months (31%). For bone scan the recommendation is every six-months (59%).

For docetaxel/cabazitaxel, the panel (79%) recommends PSA measurement every three to four weeks. The panel also recommended regular CT scans and bone scans, with a frequency of every two to four months (66%).

With regard to radium-223 and sipuleucel-T, the panel was split about the recommendation for PSA measurement and imaging.
C. Stopping treatment

The panel stressed that survival-prolonging treatment should not be stopped for PSA progression. We suggest that at least two out of PSA, radiographic, or clinical progression, should be fulfilled to stop treatment.

7. Use of osteoclast-targeted agents for SRE and SSE prevention in CRPC (partial consensus)

Panel majority (62%) supports that CRPC patients should receive an osteoclast-targeted agent for prevention of SRE.

There is no agent preference and we are almost equally divided between zoledronic acid (30%), denosumab (42%), or either of the two options being used (27%).

The same consideration regarded frequency of treatment administration for zoledronic acid or denosumab. The panel recommends all three approaches, i.e. dosing every three to four weeks or a less frequent administration from the beginning or alternatively recommend a three to four weekly dosing for about two years and less frequently after that. The panel was divided between two years versus indefinite use.

In CRPC with no bone metastases the panel (88%) does not recommend an osteoclast-targeted agent for delaying onset of bone metastases.

Zoledronic acid and denosumab are both approved for prevention of SRE: In the pivotal trial by Saad et al, zoledronic acid was given at a dose of 4 mg every three weeks for a total of 20 cycles (15 months) with an option to continue for an additional nine months extension (24 months) (Saad JNCI 2002 und 2004). Denosumab tested dose was 120 mg subcutaneously every four weeks until discontinuation or until the primary cut-off date, (Fizazi Lanc 2011).

The optimal timing for starting the treatment, optimal treatment intensity (dose and frequency), and optimal duration of osteoclast-targeted agents for CRPC patients is unclear.

8. Predictive markers and clinically important factors for decision-making in daily clinical practice (consensus)

The panel stressed the need for predictive markers indicating sensitivity or resistance to a specific therapy. The panel (94%) is of the opinion that at present there is no single predictive factor to be used in daily clinical practice that is validated and established as a predictive factor for treatment choice for CRPC patients.

Factors arguing for chemotherapy instead of survival prolonging endocrine agents were discussed. The panel is of the strong opinion, that a Gleason score of ≥8 (88% no) and a circulating tumour cell count (CTC) of ≥5/7.5 mL (91% no) as single factors do not necessarily influence this decision. Also, in patients with extensive disease on imaging, 67% of the panel was of the opinion that this factor alone should not influence treatment choice.

For several other factors, the panel was divided whether these factors would favour chemotherapy (yes) instead of abiraterone or enzalutamide: expression of AR-splice variants (47% yes, 44% no), presence of visceral metastases (50% yes, 50% no), short response (≤12 months) to primary ADT (53% yes, 47% no) and low PSA (<20), and high tumour volume (65% yes, 35% no).

In daily clinical practice decision-making is based on multitude of patient and tumour-related factors as well as physician preference and the cost and availability of drugs.
8.1 Tumour biopsy

Fresh tumour biopsies in CRPC patients are increasingly incorporated into clinical trials and advances in imaging and laboratory technologies have made the processing of biopsies also from bone metastases feasible (Spritzer CE Radiology 2013; Efstathiou E, Eur Urol 2015 and Efstathiou E, JCO 2012, Ferraldeschi R Eur Urol 2015).

However, it is unclear in daily clinical practice when a biopsy in a CRPC patient should be considered. In this circumstance tumour biopsies should only be performed if the procedure can be done without unreasonable risks, if adequate handling and analysis of the tissue is ensured, and if the result has potential implications on patient management. It is recognised that in a subset of CRPC patients a canonical AR signalling-independent phenotype may develop which can be associated with rapidly progressing visceral metastases, predominately lytic bone metastatic disease, and stable or low PSA levels. Recommendations on the diagnosis of this phenotype have recently been published (Beltran H CCR 2014). It is still unclear what the optimal treatment is in these patients but platinum-based therapy is often recommended.

The panel discussed a number of clinical factors that may indicate that a tumour biopsy should be considered, namely low PSA (<20) and high tumour volume (44% yes in the majority, 47% in a minority, 9% no), new development of visceral metastases (32% yes in the majority, 56% in a minority, 12% no), the progressive lesions in case of discordant tumour response to treatment (49% yes in the majority, 46% in a minority, 6% no), predominately lytic bone metastatic disease (37% yes in the majority, 37% in a minority, 26% no) in a patient progressing on primary ADT within < six months (23% yes in the majority, 31% in a minority, 46% no).

9. Oligometastatic castration-naive prostate cancer

This disease stage is becoming increasingly an area of interest with potential benefit from combined management. The panel (85%) defined oligometastatic disease as the presence of ≤ three synchronous metastases (bone and/or lymph nodes).

The panel does not recommend local treatment of the primary tumour and all metastases without (ADT). Combination with ADT can though be considered.

In case of relapse with oligometastatic disease after radical local treatment 58% of the panel do not recommend local treatment of all metastases instead of systemic treatment (ADT) but 39% of the panel would consider it in a minority of selected patients. In the context of additional ADT (temporarily given) 27% of the panel do not recommend local treatment of all metastases, 46% of the panel recommend it in a minority of selected patients, and 27% of the panel recommends this treatment in the majority of patients.

10. Management of patients in general

Treatment of men with advanced prostate cancer has become much more complex in recent years. Real multidisciplinary consult is crucial for optimal patient care.

Half of the panel members recommend that patients should be discussed in a multidisciplinary team (MDT) before a new line of therapy is started and 44% recommend discussion at the MDT in a minority of selected patients. Although the importance of MDTs is acknowledged, time constraint is the main reason for not discussing all cases but only complex patient cases in an MDT. There are also clear differences between different health systems, since in some countries discussion in a MDT is a prerequisite for insurances to cover the costs of the treatments.

The panel (94%) recommended that patients should be informed about the possibility of participating in a clinical trial to improve knowledge of the disease.

A majority of the panel (64%) also recommended early access for CRPC patients to an expert in symptom palliation or a dedicated palliative care service.
Conclusion

This first consensus meeting was embraced by our community with enthusiasm. Our meeting room was flooded with physicians involved in the question and answer process. It was a very exciting experience for all of us and the organisers Silke Gillessen and Aurelius Omlin should be commended for this.

The support by PCF and Europa Uomo reinforced our sense of obligation to offer the highest level of service possible and I am confident we delivered to the best of our ability.

This was a truly amazing ‘dream team’ coming together and I was honoured to be part of it. As we say here at MD Anderson, I felt that we are all making cancer history in a moment.

In some areas there was clear consensus amongst the prostate cancer experts whereas in other topics there were diverging opinions reflective of unmet needs in our field. Could we do better? …by all means we can and we will. Thanks to the community's support and feedback, as we have more meetings we will certainly be able to improve the care and treatment of prostate cancer.