THE MANY FACES OF MCRPC: ASSESSING PATIENT PROFILES AND TAILORING TREATMENT IN A CHANGING THERAPEUTIC LANDSCAPE

Summary of Presentations from the Bayer Healthcare Symposium, held at the 29th Annual EAU Congress, Stockholm, Sweden, on 11th April 2014

Chairperson

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MEETING SUMMARY

The Bayer-sponsored satellite symposium brought together a range of experts in the field of metastatic castrate-resistant prostate cancer (mCRPC), including Professors Fred Saad, Joe O'Sullivan, Anders Bjartell, Wolfgang Loidl, and Manfred Wirth. This distinguished faculty came together to discuss the changing paradigm and therapeutic options available in the management of mCRPC, offering the opportunity for interactive audience participation to discuss the current treatment landscape.

Understanding the Unmet Needs and Treatment Options in mCRPC: A Rapidly Changing Field

Professor Fred Saad

Prof Fred Saad began his presentation by introducing the audience to the different prostate cancer disease states. These range from patients with localised prostate cancer to those experiencing advanced disease with primary prostate-specific antigen (PSA) failure, and those who progress to develop CRPC following second PSA failure.

Treatment options available before 2010 constituted largely supportive agents including androgen deprivation therapy (ADT) and docetaxel, which was the first agent to show improvements in overall survival; ultimately however, patients would eventually succumb to mCRPC.[1] Recently, the treatment of mCRPC has evolved with Phase III studies showing efficacy as well as improvements in both quality of life and survival with several drugs that precede docetaxel or that may be used as a replacement.

Prof Saad presented data from the pivotal TAX327 study in which docetaxel (plus prednisolone)

demonstrated improved long-term survival when given to patients every 3 weeks versus mitoxantrone and prednisone.[2] In addition to these data, administration of cabazitaxel (plus prednisolone) in patients previously treated with docetaxel resulted in a 30% reduction in the risk of death, and a 2.4 month improvement in overall survival in patients who were currently taking docetaxel or had previously taken docetaxel.[3] Similarly, the administration of abiraterone and prednisolone in mCRPC patients who have already received chemotherapy, resulted in a 4.6 month improvement on overall survival with a 26% reduction in the risk of death.[4] The 2012 AFFIRM study confirmed that targeting the androgen receptor is a reasonable approach; use of enzalutamide after chemotherapy led to a 36% reduction in the risk of death and a 4.8 month improvement in overall survival.[5]

Prof Saad went on to present recent data from a Phase III study during which chemotherapy-naïve patients received abiraterone in combination with prednisolone. This not only showed a 5 month improvement in overall survival, but also doubled radiographic progression-free survival (PFS) when compared to prednisolone alone; however, the results did not achieve statistical significance.[6] Most recently, the PREVAIL study, which included asymptomatic or slightly symptomatic patients treated with enzalutamide versus placebo has reported an increased overall survival of 2.2 months and an 81% improvement in radiographic PFS.[7] Prof Saad also considered results from the IMPACT trial; in asymptomatic or slightly symptomatic patients, sipuleucel-T increased overall survival; however, in contrast to enzalutamide, there was no effect on PFS or PSA response.[8] Finally, in the ALSYMPCA trial, Radium-223 showed a 3.6-month improvement in median overall survival, providing a meaningful option for patients pre or post-chemotherapy.

Bone metastasis is a recurrent problem in patients with mCRPC, occurring in 90% of this patient population. The consequences of bone metastases are skeletal related events (SREs), which are associated with increased mortality, increased pain and hospitalisation, and decreased mobility and quality of life.[9,10] Therefore, reducing the rate of SREs is an important step in improving disease burden in patients with CRPC, supported by data that suggest that fractures negatively affect survival.[11,12]

Prof Saad concluded his talk by summarising the current available therapeutic agents, emphasising that clinical trials remain an important and active area of research. He emphasised that combining these various therapies and using them correctly on an individual patient basis is the key to reducing complications of CRPC and improving long-term survival.

Energising the Treatment Landscape: Efficacy and Safety of a New Alpha-Emitting Radiopharmaceutical in mCRPC

Professor Joe O'Sullivan

Prof Joe O'Sullivan began his presentation by introducing Radium-223, an alpha-emitting pharmaceutical, which is a radioactive isotope of radium and a calcium mimetic. It is able to target bone metastasis by generating highly localised, intense radiation zones that induce non-repairable, double-strand DNA breaks.[13]

He went on to describe data from ALSYMPCA, a Phase III clinical trial in which mCRPC patients, with at least two symptomatic bone metastases, were treated with Radium-223 and best standard of care versus best standard of care alone.[11] Treatment duration was 6 months and patients were followed-up for 3 years. Results showed that treatment with Radium-223 significantly reduced the risk of death by 30% and improved overall survival by 3.6 months, regardless of previous treatment received. In addition to this, systematic skeletal events (SSEs) were delayed by 5.8 months in these patients. There was an increase in quality of life scores as assessed by the FACT-P scoring system.[14] Examination of adverse events in this trial revealed that Radium-223 is very well tolerated: Grade 3/4 side-effects were comparable between the Radium-223 and the placebo group.

Prof O'Sullivan concluded his talk by suggesting that Radium-223 may provide a new standard of care for the treatment of patients with CRPC and bone metastasis. By targeting bone metastases, Radium-223 has shown improved overall survival and time to SSE, reduced pain, and increased QoL. In particular, its high affinity for osteoblastic bone metastases and predominant gastrointestinal excretion, as well as no close-contact restrictions required after therapy, make it an ideal first-in-class candidate for mCRPC.

Examining Biomarkers in the Management and Treatment of Patients with mCRPC

Professor Anders Bjartell

Prof Anders Bjartell opened his session by introducing the idea of the use of predictive biomarkers in improving disease outcomes in mCRPC. The presentation began on an interactive platform during which the audience were asked if they used either alkaline phosphatase (ALP) or PSA as a prognostic or predictive biomarker in the mCRPC setting. It continued with a discussion about the correlation between these two markers and the subsequent therapeutic success.

The PSA response rate to therapy is limited and varies greatly with different therapies, ranging from 54% with enzalutamide to just 3% with sipuleucel-T, suggesting that clinical benefit may not necessarily correlate with PSA decline.[5,8] This variation is largely dependent on the mechanism of action of the therapy used; therapies that target androgen action may result in higher levels of PSA decline as PSA is directly regulated by androgen receptors.[15] Therefore, PSA should be used with other prognostic markers in order to establish a patient's response to therapy.[1,16,17]

Another prognostic marker, ALP, is elevated in most patients with bone metastases and baseline ALP provided prognostic information in mCRPC, with reductions in total ALP reflecting biological changes in bone turnover and osteoblastic activity.[18] Despite this, it remains to be determined whether elevations in ALP levels are a true predictor of the benefits of a therapy that treats bone metastases.[19] Prof Bjartell presented results from the pivotal ALSYMPCA study, in which Radium-223 treatment significantly reduced total ALP and PSA levels by 30%.[11] In addition to this, ALP decline was associated with an overall increase in survival in patients treated with Radium-223.[20]

Prof Bjartell concluded that ALP may provide important prognostic information in mCRPC and that further ongoing analyses may shed further light on whether this biomarker is indeed a useful indicator for treatment response.

Exploring the Patient Journey in mCRPC via Interactive Case Studies

Professor Wolfgang Loidl

Prof Wolfgang Loidl commenced his talk by outlining the treatment journey in Austria, where there is an established PSA screening programme to detect early CRPC. However, PSA testing has been reported to decline over the past 2 years due to unqualified controversy in the media. Within his presentation, Prof Loidl utilised his own clinical cases to illustrate key points of the discussion.

Prof Loidl went on to discuss a patient case study of a 60-year-old male patient diagnosed with CRPC in 1991. At this time only very limited therapeutic options were available. The patient was subsequently treated with a regimen of radiotherapy to the prostate and pelvic lymph nodes but the tumour returned. The patient received hormone therapy and PSA levels were brought down to 0.0 ng/mL. In 2009, the tumour returned again with a PSA of 1.8 ng/mL. As a regime of hormone and radiation therapy and surgical intervention was ineffective, the patient was given a second round of hormone therapy (bicalutamide and gonadotropin-releasing hormone [GnRH]). Although the patient had no symptoms, a single spot was still observed in the ileum and he was subsequently treated with docetaxel (plus prednisolone) and denosumab, which brought his PSA levels down from 5.5 ng/mL to 2.0 ng/mL. Clinicians in the audience were invited to discuss the treatment plan that they would embark on in the case of this patient, with varied responses ranging from continuing therapy to re-assessment of the patient's condition. Chemotherapy was stopped after three cycles, following which PSA levels rose to 30 ng/mL. This was followed by two more cycles of docetaxel (plus prednisolone) therapy after which the patient requested a break from chemotherapy.

After this break, the patient returned to the clinic with a PSA of 122 ng/mL and heavy pain; however, the patient refused chemotherapy. The audience went on to discuss treatment options available to patients who are averse to chemotherapy. Providing a follow-up, Prof Loidl informed that unfortunately the patient subsequently died of mCRPC a few months later.

Professor Loidl continued with the presentation of a second case of a 68-year-old male diagnosed with CRPC in 2007. The patient received ADT in combination with radiotherapy. His PSA levels were 0.9 ng/mL 1 year following the commencement of therapy. These rose from 1.5 ng/mL to 4.1 ng/mL, prompting a restart of ADT. Within a year, his PSA levels were down to 0.7 ng/mL. Within 2 years, the patient showed multiple lesions in the spine and a PSA level of 10 ng/mL. The audience was asked how best to proceed with this patient and concerns were raised about the lack of correlation between PSA levels and the severity of disease, with a possible indication that the patient may have neuroendocrine differentiation.

Continuing with the case, the audience learned that the patient went on to receive docetaxel (plus prednisolone) but requested a break from chemotherapy for 2 months. The patient's PSA levels increased to 35 ng/mL and bone pain returned. Docetaxel (plus prednisolone) therapy was then resumed following the progression of bone metastasis and increasing pain. The PSA level of the patient continued to rise and was accompanied by increasing pain. In contrast to the previous case, at this time several new therapies provided treatment options for this patient. From April to September 2013, the patient received abiraterone therapy (plus prednisolone); however, he continued to experience pain and increasing PSA levels. Cabazitaxel (plus prednisolone) therapy was initiated from September to November 2013 resulting in a further increase in PSA levels from 353 to 1,232 ng/mL. Circulating tumour cell counts (CTCs) were 155 and the patient was in pain. In December 2013, Radium-223 therapy was initiated. Previously, Radium-223 was not available as European Medicines Agency (EMA) approval was obtained in November 2013 and the product was launched for the first time in Austria in December 2013. After only three cycles of Radium-223 therapy, PSA levels for this patient decreased from 1,232 to 709 ng/mL, a reduction in CTCs was seen from 155 to 22, and there was a marked reduction in pain. The positron emission tomography computed tomography scan showed stabilisation of bone lesions. Prof Loidl concluded his talk by summarising the patient's treatment journey, highlighting Radium-223 as a potential therapeutic option for patients with mCRPC and symptomatic bone metastases.

The mCRPC Treatment Continuum: Analysing Typical Patient Profiles. Questions from the Floor, Final Remarks, and Meeting Close

Professor Manfred Wirth

Prof Manfred Wirth concluded this session on mCRPC management with an overview of the currently available therapies. Similar survival benefits for newer therapies range from 3.6 months to 5.8 months in chemo-naïve and chemo-treated patients, respectively.[11,12,14] Prof Wirth compared the newer available agents with those that are currently best in standard of care, showing data which suggest that although both sets of agents have similar survival benefit in mCRPC patients, they have very different safety profiles.[2,7,8] These similar levels of overall survival are important when considering adjusting a patient's treatment regime.

In particular, the encouraging efficacy and safety profile of Radium-223 suggests that this agent may be considered as a potent anti-tumour agent for patients with mCRPC and symptomatic bone metastases. Its ability to significantly improve overall survival, prolong time-to-first symptomatic skeletal event, and increase quality of life, make it a promising future therapy, as recommended by the EAU and the National Comprehensive Cancer Network.[21,22]

Prof Wirth drew this session to a close by stating that the changing treatment modalities in mCRPC therapy have given clinicians and patients multiple treatment options. Treatment decisions should ideally include consideration of the patient profile, clinical symptoms, and patient preference in order to develop a regime that can offer optimal clinical benefit.

This symposium highlighted important treatments in the field of mCRPC that are continually evolving. In particular, the treatment of bone metastasis, which is a major cause of morbidity and mortality in mCRPC patients, has been shown to improve long-term survival. The ongoing clinical development of newer therapies will increase understanding of the best way to optimise treatment in patients with metastatic cancers.

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