Combination treatment in metastatic prostate cancer: is the bar too high or have we fallen short?

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Abstract
Androgen deprivation therapy (ADT) alone has been the cornerstone of treatment for patients with newly diagnosed metastatic prostate cancer for the past century. Based on results from landmark trials in the past decade, combination approaches of ADT with chemotherapy or novel hormonal agents have established a new standard of care for these patients. This paradigm shift in treatment has been reflected in the updates to guideline recommendations of major professional associations. However, real-world data from around the world have highlighted the dismal adoption of combination therapy, despite evidence-based recommendations. The disparity between evidence and practice is concerning, especially with emerging evidence of survival benefit with further treatment intensification using triplet combinations (ADT, docetaxel and novel hormonal agents). Thus, a pressing need to raise awareness and call the uro-oncology community to action exists to deliver evidence-based care for these patients.

Introduction
Prostate cancer is a substantial cause of mortality for men worldwide and was the third most commonly diagnosed malignancy globally in 2020 according to the WHO1. Prostate cancer is a notoriously heterogeneous disease with wide disparity between mortality and incidence rates1. Metastatic disease can present either de novo, at diagnosis, with rates correlating with the prevalence of PSA screening in the corresponding geographic area, or in men who experienced failure of primary definitive treatment1. Nonetheless, this denomination includes a heterogeneous population of tumours ranging from indolent to highly aggressive phenotypes. However, a common aspect of all prostate cancers is being androgen driven, and androgen deprivation therapy (ADT) has been the mainstay of treatment for men with metastatic prostate cancer since the 1940s2. After an initial response to ADT, all patients with metastatic prostate cancer ultimately progress to a terminal disease state of castration resistance, and a median overall survival (OS) of ~42 months has been reported in patients treated with the traditional approach of ADT alone3,4.

The treatment landscape of metastatic prostate cancer has evolved tremendously in the past two decades, driven by parallel advancements in the understanding of tumour biology as well as the development and approval of various new agents, starting with the FDA approval of docetaxel for metastatic castration-resistant prostate cancer (mCRPC) in 2004 (ref.5). Since this first approval, the efficacy of several other classes of drugs has been established in the treatment of patients with mCRPC6,7,8,9,10, improving survival and defining a new standard of care for these patients11.

In the past decade, a paradigm shift occurred towards treatment intensification in the early stages of the disease trajectory12 using several androgen receptor pathway inhibitors (ARIs), in addition to ADT, which have been indicated for the treatment of mCRPC. This shift

was supported by evidence showing the inferiority of ADT monotherapy compared with the combination of ADT with novel hormonal agents (NHAs)13,14,15. Similarly, chemotherapy used to be reserved for the treatment of patients with mCRPC, but well-established data now show survival benefit in selected patients with metastatic hormone-sensitive prostate cancer (mHSPC) with high-volume metastases who received upfront chemotherapy upon diagnosis2,16. This evidence supported the concept of early combination therapy in patients with mHSPC.

A mature body of evidence supports upfront combination treatment with ADT in combination with an ARI (abiraterone acetate, enzalutamide or apalutamide) or docetaxel in men with mHSPC, but real-world data have shown a glaringly low rate of adoption of this doublet therapeutic regimen in clinical practice. In many countries around the world, this strategy is only used in less than half of patients who are eligible for treatment intensification17.

In this Perspective, we review the data on the poor adoption of combination treatment in clinical practice, and explore factors that might account for this trend.

Landmark trials for combination therapy

One of the earliest landmark trials to shape the therapeutic landscape in mHSPC came in 2015. In the CHAARTED trial, in which 790 patients with mHSPC were randomized to receive either ADT alone or in combination with docetaxel, the median OS was 13.6 months longer in patients with mHSPC treated with the combination of ADT and docetaxel than in patients treated with ADT alone; progression-free survival (PFS) of 20.2 months and 11.7 months was reported in patients treated with the combination therapy and ADT alone, respectively2. Similarly, in the STAMPEDE trial, an OS benefit was observed in patients treated with upfront chemohormonal therapy; in this study, median OS was 71 months (interquartile range 32 — not reached) and 81 months (interquartile range 41 — not reached) in patients treated with ADT alone and ADT plus docetaxel, respectively (HR 0.78, 95% confidence interval (CI) 0.66–0.93; P = 0.006)16. Promising results from the LATITUDE trial showed an OS benefit in patients with mHSPC treated with abiraterone acetate and prednisolone compared with patients treated with ADT plus dual placebos (HR 0.62, 95% CI 0.56–0.78, P < 0.0001)15. These results were confirmed in the adaptive, multi-arm, multi-stage STAMPEDE trial (arm G) in which a total of 1,917 patients with prostate cancer were randomized to receive ADT alone or ADT plus abiraterone acetate (1,000 mg daily) and prednisolone (5 mg daily). Among the 1,002 patients (52%) with metastatic disease, prolonged survival was observed in patients receiving combination therapy compared with ADT alone (HR 0.61, 95% CI 0.49–0.75)18. Results from these studies heralded the era of next-generation ARIs for early treatment of patients with newly diagnosed mHSPC, and in the following years, two additional ARIs (enzalutamide and apalutamide) were introduced with convincing OS and PFS benefit13,14 (Table 1).

The effect of ARIs on OS has been very consistent among different trials (Table 1), and results from these studies collectively strongly support doublet combination treatment with ADT plus abiraterone acetate, enzalutamide or apalutamide, which were proven to be life prolonging for patients with mHSPC in the early stages of disease. Considering the benefits

of treatment with chemotherapeutics and ARIs in combination with ADT in patients with mHSPC, the synergistic effect of triplet therapy with these agents was explored (Table 2).

In three landmark randomized phase III trials — ARCHES13, ENZAMET19, and TITAN14 — patients with mHSPC were randomized to receive ADT or ADT in combination with enzalutamide (ARCHES and ENZAMET) or apalutamide (TITAN). The difference between ARCHES and ENZAMET is in the comparator used in addition to ADT, which was a placebo in the ARCHES study, and a standard non-steroidal anti-androgen drug (bicalutamide, nilutamide or flutamide) in ENZAMET. Differently from ARCHES and TITAN, 65% of patients who received docetaxel in the ENZAMET19 study received concurrent treatment with enzalutamide during the period of chemotherapy instead of sequential treatment (docetaxel before ARIs, as occurred in the other two trials). Subgroup analyses of patients in the ARCHES, ENZAMET and TITAN trials who received docetaxel before randomization to enzalutamide or apalutamide treatment arms provided the first insights into the efficacy of triplet therapy. In these trials, no clear OS benefit was observed when docetaxel was added to doublet combination therapy with ADT plus ARIs (enzalutamide or apalutamide) (Table 2). However, the proportions of patients treated with docetaxel in these trials varied, ranging from 10.7% in the TITAN14 study to 17.8% in ARCHES13 and 14.1% in ENZAMET19; the decision to treat patients with docetaxel was not dictated by the trial protocol but was made by clinicians and, therefore, did not always correlate with tumour volume or risk. Thus, a considerable heterogeneity in the use of docetaxel was reported in these studies, which could have biased the subgroup analyses.

The PEACE-1 trial was the first study in which OS benefit with triplet therapy was shown. In this study, the benefits of adding abiraterone to the combination therapy of ADT plus docetaxel were investigated20. The original design of this prospective, randomized, phase III study did not specifically include docetaxel; however, docetaxel was permitted as part of standard-of-care treatment in 2015, after the results of the CHAARTED trial were reported, and was made compulsory from 2017 onwards. Treatment with the triplet combination therapy provided a median of 2.3 years advantage in radiographic PFS (HR 0.54, 95% CI 0.46–0.64, $P < 0.0001$) and significantly improved OS (HR 0.75, 95% CI 0.59–0.95, $P = 0.017$), which were the primary end points of the study. The survival benefit was more prominent for patients with high-volume disease (HR 0.72, 95% CI 0.55–0.95, $P = 0.019$), than for patients with low-volume disease (HR 0.83, 95% CI 0.5–1.38, $P = 0.66$)20.

ARASENS is a randomized phase III trial in which the triplet combination of darolutamide with docetaxel and ADT versus docetaxel and ADT alone was investigated21. Results from this study showed that triplet combination therapy significantly reduced the risk of death by 32.5% (HR 0.68, 95% CI 0.57–0.8, $P < 0.001$), and this benefit was consistent across pre-specified subgroups of patients. Improvements in the secondary end points of the study, which were time to CRPC and time to pain progression, were also observed in patients treated with triplet therapy (HR 0.36, 95% CI 0.30–0.42, $P < 0.001$ and HR 0.79, 95% CI 0.66–0.95, $P = 0.01$, respectively). The rates of adverse events were similar in both study arms (44.8% versus 42.3%).

In summary, several randomized phase III trials have provided level 1 evidence for the upfront use of combination therapy in patients with mHSPC. The efficacy of adding

docetaxel or abiraterone to ADT was shown in the CHAARTED and LATITUDE studies, whereas results from the ARCHES and TITAN studies supported the addition of enzalutamide and apalutamide to ADT, respectively. Triplet therapy with ADT, docetaxel and an ARI in patients with mHSPC was assessed in the PEACE-1 and ARASENS trials and, in both studies, the oncological benefits of the concurrent use of ADT, docetaxel and abiraterone acetate or darolutamide, respectively, were shown.

Guidelines

Various major professional bodies and societies adjusted recommendations for the optimal management of patients with mHSPC based on evidence of the efficacy of early combination treatment of ADT with ARIs or docetaxel. Considering the high-level evidence from the STAMPEDE and CHAARTED trials, a strong recommendation for castration combined with chemotherapy (docetaxel) for all patients with M1 disease and who are fit enough for chemotherapy was added in the 2017 version of the European Urology Association (EAU) guidelines22. In the subsequent edition of the guidelines in 2018, abiraterone acetate with prednisolone was strongly recommended to all patients with newly diagnosed de novo metastatic disease, based on data from the LATITUDE trial23. The current guidelines have adopted a firm tone in advocating combination therapy in patients who are fit to receive this treatment, and categorically state that ADT alone should not be offered to patients with newly diagnosed metastatic disease who are willing to receive upfront combinations agents and have no contra-indications for this therapy22.

Similar to EAU, recommendations based on high-level evidence from the available clinical trials were introduced in the 2020 guidelines from the American Urological Association24, in which upfront combination therapy, either with new hormonal agents (abiraterone acetate, enzalutamide, apalutamide) or with docetaxel, were supported.

In the current guidelines from the National Comprehensive Cancer Network25, these combination treatment options were introduced as category 1 recommendations based on the high-level evidence from clinical trials.

Notably, none of the guidelines has made a distinction between the hormonal agents and docetaxel owing to the lack of strong evidence showing superiority of one treatment over the other. Available data provide no potential for direct head-to-head comparisons between the two classes of therapeutics, and the best level of evidence currently comes from indirect comparisons in network meta-analyses26,27. In a network meta-analysis of nine randomized controlled trials including 9,960 patients with mHSPC, treatment with abiraterone, docetaxel and enzalutamide resulted in improved OS compared with ADT alone (HR 0.83, 95% credible interval (CrI) 0.76–0.90; HR 0.90, 95% CrI 0.82–0.98; and HR 0.85, 95% CrI 0.73–0.99, respectively) with no differences among the three agents28. PFS was improved in patients treated with abiraterone, apalutamide and enzalutamide compared with patients treated with docetaxel (HR 0.85, 95% CrI 0.78–0.93; HR 0.87, 95% CrI 0.77–0.98; and HR 0.80, 95% CrI 0.73–0.88, respectively), and enzalutamide was shown to have the highest likelihood of providing the maximal PFS in a treatment ranking analysis28. The superiority of ARIs over docetaxel in improving PFS is in agreement with previous network meta-analyses26,27. With regard to adverse effects, apalutamide was highly likely to have the lowest rate of adverse events compared with abiraterone and enzalutamide28.

Real-world practice patterns

Robust data on the efficacy of upfront combination therapy have been presented in the past few years, but real-world data show a dismal uptake of evidence-based recommendations. Insights into the real-world usage of combination therapies in mHSPC were presented in a study in which a decade's worth (2009–2018) of data from an American Medicare database including 35,194 men with mHSPC were analysed29. Results from this study showed that 76.4% of patients received ADT monotherapy as a first-line treatment. Results from a chronological sub-analysis of data showed that the majority of patients continued to receive ADT alone (70.5% in the 2017–2018 time period), although results on the efficacy of ADT combination with docetaxel and abiraterone acetate plus prednisolone from CHAARTED and LATITUDE trials were reported in 2015 and 2017, respectively, and these two agents were available. The decline in the use of docetaxel, even after results from CHAARTED were published in 2015, could be explained, in part, by the slight increase in the use of NHAs. However, only 13.4% of patients were treated with combination of ADT with docetaxel or NHAs, indicating that overall, the rate of treatment intensification was still very low, regardless of the agent used29. This pattern of low use of combination therapy was confirmed in another study30 in which data from the US Veteran's Health Administration were analysed, and a similar high rate of patients treated with ADT monotherapy alone (62%) was shown.

Similar to what was observed in the USA, a post CHAARTED and LATTITUDE analysis of data from a large population-based cohort study from Canada showed that only 13% of patients with de novo mHSPC received combination treatment with abiraterone acetate and prednisolone or docetaxel, whereas ~80% of patients only received conventional ADT alone31.

A global picture of real-world treatment patterns, including retrospective data from the IPSOS Global Oncology Monitor Database captured in the USA, Europe and Asia over 3 years (January 2018 to June 2020), was presented at the ESMO 2021 conference. Although these data are not yet published in a peer-reviewed journal, results from this retrospective cross-sectional study showed again that use of androgen synthesis inhibitor (14.3%) and second-generation AR inhibitors (5.6%) was relatively infrequent. Lower rates of usage of taxane chemotherapy were reported in the USA and in Japan (8.5% and 0.2%, respectively) than in Europe and China (Germany, 17.0%; France, 15.0%; China 13.4%)17.

An encouraging trend of increasing use of docetaxel in the years following the publication of results from the CHAARTED trial was observed in a study in which predictors of real-world usage of combination treatment with docetaxel and ADT were assessed in patients with mHSPC in Australia32. Data from this study showed that the use of docetaxel increased from 20% in 2014 to 33% in 2018; young age and treatment at a private hospital were predictors of increased usage of docetaxel32. However, the treatment regime for the majority of patients (67%) still did not include docetaxel, and approximately half of the patients received ADT alone32. Results from a real-world study in which uptake rates of docetaxel were assessed in patients in the West of Scotland Cancer Network showed that ~62% of patients with newly diagnosed metastatic prostate cancer received ADT alone, despite discussion during multidisciplinary meetings33. These data report the suboptimal

utilization of combination therapy consisting of ADT with either ARIs or docetaxel in the real-world setting, and highlight the deviation of real-life practice from evidence-based treatment recommendations for patients with mHSPC.

Potential reasons for low uptake of combination therapy in clinical practice
Considering the high-level evidence generated in clinical trials, what could explain the observed lack of uptake of combination therapy in real-world settings? Clinicians would be expected to have bolstered confidence offering this new standard of care, particularly with the explicit recommendations included in the guidelines.

Clear consensus on this new therapeutic strategy was reached at the 2021 Advance Prostate Cancer Consensus Conference. With regard to patients with newly diagnosed, high-volume mHSPC, unanimous agreement was reached on escalation of treatment, and all panellists voted for some form of treatment intensification: 49% of panellists voted for the combination of an ARI (abiraterone, apalutamide or enzalutamide) with ADT; 11% voted for a chemohormonal combination of docetaxel with ADT; and 40% voted for triplet therapy (ARI and docetaxel with ADT). No one voted for treatment with ADT alone. For patients with low-volume mHSPC, 96% of panellists advocated for combination treatment, and only 4% chose ADT alone34. Similar conclusions were reached during a 2019 consensus statement from south-east Asia on the management of patients with metastatic prostate cancer in which the use of the combination of ADT with abiraterone as upfront treatment was strongly supported (76.9% of panellists) for patients with de novo mHSPC. The panel also supported reimbursement of abiraterone given as a first-line treatment to increase the number of patients who can receive this therapy35.

Clearly, clinical evidence, guideline recommendations and consensus amongst clinicians about the care of patients with mHSPC are well aligned. Evidence-based practice is the ideal standard of care, but oversimplifies the practice of medicine and health-care delivery, as a multitude of factors beyond the clinical evidence supporting the efficacy of a drug need to be considered before patients can ultimately receive the recommended treatment. These factors accounting for the discordance in rates of combination therapy observed globally probably lie further downstream in the patient's care path.

Patient access to therapy is governed by several factors such as cost and reimbursement models, availability of the therapeutic agents and geographical location-specific health economics, all of which might substantially vary among countries. If the differences in the real-world usage of combination therapy were a result of cost alone, an increased use of docetaxel, which has been shown to be a more cost-effective option than other therapies in mHSPC treatment, would be expected36,37. However, the proportion of patients with mHSPC treated with docetaxel in the USA has been well under 20% in the years up to 2019 (refs.38,39). Age is an independent predictor of increased usage of docetaxel, as shown in one study32 in which 64% of patients <70 years of age received docetaxel. Conversely, results from another study showed that, although rates of docetaxel usage were threefold higher in young patients (<75 years) than older patients (>75 years), uptake of this therapy was still dismal (6.8% of patients)38.

Regulatory and reimbursement approvals also have an important role in determining patient access to therapy. Data show a wide variation in reimbursement times for new drugs amongst European countries, which contributes in part to eventual uptake and access in eligible patients40,41. The effect of this inequality in cancer care can be seen in the control arm of the LATITUDE trial. In this study, abiraterone was not provided by the trial in the CRPC setting; thus, local access determined whether patients in the control arm could benefit from abiraterone at disease progression15. The difference of 8 months in OS between patients from Eastern Europe, where abiraterone was available, and patients from Western Europe, where the access to abiraterone was limited, provided evidence of the direct effect of differential drug access on patient outcomes. Thus, several organizations have put efforts to tackle these issues and optimize cancer treatment and outcomes at a population level. In 2021, the European Commission presented the Europe's Beating Cancer Plan, a comprehensive strategy to enhance cancer survivorship with flagship initiatives and action plans that include ensuring access to innovative cancer diagnosis and treatments, and reducing cancer inequalities across the EU42. Similarly, the European Cancer Organization formed a network to work on aims such as addressing patient-centric public health needs and ensuring equitable cancer care and delivery across Europe43. These massive initiatives will undoubtedly help to optimize patient access to effective treatments for mHSPC.

In the report from the first global Prostate Cancer Consensus Conference for Developing Countries, concerns about resource limitation for clinicians in developing countries faced with decision making in the treatment of mHSPC were raised. In a best-practice scenario, 64.9% of panellists voted for combination therapy of ADT with abiraterone. This response drastically dropped to 8.1% when the panellists were asked to consider practice in a setting of limited resources44. Moreover, in a setting of limited resources, panellists' responses also favoured ADT by orchiectomy alone and ADT in combination with docetaxel purely considering costs, highlighting how a physician's decision and treatment patterns can be influenced by health economics44.

Cancer survival and outcomes have been shown to vary widely according to geographic location owing to socio-economic challenges reported in rural areas, which might affect optimal cancer treatments45,46. The fact that experts in consensus meetings push for adherence to best practices is reassuring, but these opinions and responses come primarily from practitioners in centralized, high-volume academic institutions, which are often over-represented in these consensus meetings. Thus, the polls might not reflect the treatment philosophy in low-volume, resource-limited, rural communities or in certain parts of the world.

The lack of prognostic and predictive tools to improve selection of patients with mHSPC who will most benefit from treatment intensification is another important point to consider. In a study in which transcriptomic profiling of primary tumour tissues correlated with OS in 160 patients enrolled in the CHAARTED study, several potential biomarkers of treatment response were identified47. Patients with luminal B tumour subtype were shown to respond significantly better to chemohormonal combination therapy than ADT monotherapy in terms of OS (HR 0.45, P = 0.007); conversely, no OS benefit was reported in patients with basal tumour subtype, even in the presence of high-volume disease. Similarly, an increased OS benefit was observed in patients with a high Decipher risk treated with combination

therapy (HR 0.41, P = 0.015)47. These results provided early evidence supporting a potential biomarker-based selection of patients for chemohormonal therapy. In another study48, the utility of genomic copy number aberrations as a potential biomarker to guide treatment selection was assessed in patients newly diagnosed with mHSPC from the STAMPEDE trial who were randomized to receive ADT alone. Results from this study showed that patients with the lowest genomic instability receiving ADT alone had extremely favourable median OS (>10 years). Thus, the burden of copy number aberrations has a potential clinical utility in identifying patients with mHSPC with a good prognosis, who might not require treatment intensification. Prognostic biomarkers and predictive biomarkers of treatment response are important in selecting patients who might benefit the most from treatment intensification.

Upcoming combination treatment options

The trend towards low use of combination treatment impedes the generation of real-world data on the efficacy of these therapies outside of clinical trials. Additional therapeutic agents currently indicated for mCRPC are anticipated to be approved for usage in the early stages of hormone-sensitive disease as a part of combination treatment with ADT; thus, this problem is likely to worsen, considering the current pattern of low adoption rate of combination therapy with ARIs and docetaxel. The interest in harnessing synergism across different classes of therapeutics expanded with the increase in the number of available treatment options in mHSPC. The encouraging results from PEACE-1 and ARASENS trials have certainly supported the use of triplet therapy for patients with mHSPC. Results from several other ongoing trials are awaited in order to gain additional insights into the efficacy of further triplet combinations.

Poly adenosine diphosphate-ribose polymerase (PARP) inhibitors have shown efficacy in patients with mCRPC harbouring alterations in DNA repair genes49. Results from synthetic lethality studies in cellular models showed that suppression of homologous recombination repair (HRR) gene expression caused by androgen receptor inhibition increased cell vulnerability to PARP inhibitors and, in turn, PARP-dependent DNA-damage-induced cell death50,51,52. The AMPLITUDE53 and TALAPRO-3 (ref.54) trials, in which PARP inhibitors will be assessed in combination with ARIs in patients with mHSPC, are ongoing.

Treatment with lutetium-177 (177Lu)-PSMA -617 gave encouraging results in in the VISION55 and TheraP56 trials, in which patients with mCRPC previously treated with ARIs and taxane regimens and who had prostate-specific membrane antigen (PSMA)-positive disease were included; in these studies, patients treated with radioligand therapy showed improved radiographic PFS and OS (VISION trial), as well as PSA response (TheraP trial), compared with patients receiving the standard-of-care treatment. Based on these results, the efficacy of targeted radionuclide therapy as a part of triplet therapy in patients with mHSPC is being assessed in two ongoing trials. UpFrontPSMA is an open-label, randomized, multicentre, phase II trial in which the activity and safety of combination therapy of ADT with sequential 177Lu-PSMA-617 and docetaxel versus docetaxel alone is assessed in men with de novo mHSPC57,58. PSMAddition is an open-label, randomized, phase III study involving men with mHSPC, in which the efficacy of 177Lu-PSMA-617 in combination with standard-of-care therapy (consisting of ARI and ADT) is compared with standard of care alone59.

The phosphatidylinositol 3-kinase (PI3K)–AKT pathway has a pivotal role in prostate cancer and has been implicated in tumorigenesis, disease progression and mechanisms of treatment resistance60,61. In the ProCAID trial, the efficacy of combination therapy with capivasertib, a potent selective inhibitor of all three AKT isoforms (AKT1, AKT2 and AKT3), plus docetaxel chemotherapy (compared with placebo plus docetaxel) was assessed in patients with mCRPC. Overall median OS was 25.3 months in patients in the capivasertib plus docetaxel arm versus 20.3 months in patients receiving placebo plus docetaxel (HR 0.70, 95% CI 0.47–1.05; P = 0.09). Within the subgroup of patients who had previously received abiraterone or enzalutamide, OS benefit after treatment with capivasertib plus docetaxel was significantly higher than patients receiving placebo (median OS 31.1 months versus 19.3 months; HR 0.57, 95% CI 0.36–0.91). This survival benefit was not observed in patients naive to prior abiraterone or enzalutamide treatment (median OS 31.1 versus not reached; HR 1.43, 95% CI 0.63–3.23)62. In the ongoing CAPItello-281 study, the efficacy and safety of the triplet combination of capivasertib plus abiraterone plus ADT versus abiraterone with ADT is being assessed in patients with PTEN-deficient mHSPC63.

The discovery of immune checkpoint receptors and ligands led to a transformative breakthrough in cancer treatment, with the advent of immune checkpoint inhibition. Pembrolizumab, a programmed cell death 1 (PD1) inhibitor, received FDA approval in 2017 as a tumour-agnostic therapy for patients with microsatellite instability-high tumours64. Currently, no phase III data on immune checkpoint inhibitors in patients with mHSPC exist, and the results of the KEYNOTE-991 trial are awaited65. In this study, efficacy and safety of the combination of pembrolizumab, enzalutamide and ADT is being assessed in patients with mHSPC and compared with enzalutamide plus ADT therapy alone.

Intensification of treatment by combining multiple agents leads to the important question about the duration of treatment. Patient access to treatment and drug availability are important points to consider, but the optimal application of combination therapy might ultimately lie in selecting how to intensify and how to de-escalate treatment. Considering that no superiority of continuous over intermittent ADT has been established66, the feasibility of intermittent regimens should be considered after an initial period of treatment intensification in selected patients. PSA kinetics might be used as a biomarker to guide patient selection for treatment de-escalation in patients with mHSPC, considering the prognostic value of PSA in several trials67,68,69, although the absolute PSA value might not be as reliable as in the mCRPC setting. Further trials are needed to define the optimal strategy for treatment de-escalation, including timing and choice of agents for de-escalation.

Considerations

Real-world data highlight the complexities of disease treatment and help to identify many issues that might hamper best practices. Any change or innovation will be characterized by “early adopters” and “late movers” as described by E.M. Rogers in 1962 in his diffusion of innovation theory70. This theory does not capture all the issues with adoption of a new behaviour, such as resource capabilities, but helps to contextualize the issue and is appropriate in instances of poor adoption of a new standard or intervention71. Considering the low usage rates globally, adoption of doublet combination therapy (ADT plus ARIs or docetaxel) in clinical practice for patients with mHSPC seems to be in the phase of early

adoption. In the diffusion of innovation theory, the adoption of an innovation or change follows a path in which the change first starts with a small group of innovators. For example, at this stage, exploratory landmark trials can be carried out to assess the efficacy of a new treatment strategy (such as the doublet and triplet combination treatments in patients with mHSPC) (Fig. 1). This early adoption rate is then followed by an increase in the uptake of the innovation (swell of the violin plot in Fig 1), which is attributable to opinion leaders and clinicians in academic centres who are convinced by the data and incorporate the emerging intervention into clinical practice. The opposite end of the plot (bottom end) is ascribed to "late movers". The problem is that evidence of life-prolonging treatment with upfront doublet combination therapy with ARIs and docetaxel in patients with mHSPC is not early anymore, especially when considering the data for docetaxel and abiraterone from the CHAARTED and LATITUDE trials. A widespread adoption of this treatment strategy, as would be expected from the diffusion of innovation theory70, has not yet been observed, although evidence of doublet therapy efficacy is more than half a decade old. Additional evidence of treatment intensification in patients with mHSPC will be generated in the near future. Whether the rest of the community just needs additional time to catch up with the standard of care and to adopt combination therapy (both doublet and triplet combinations) on a large scale remains unknown, but for now, clinicians need to continue to uphold the standards and not lower the bar.

Conclusions

The treatment landscape for metastatic prostate cancer has evolved rapidly in the past decade, and results from several landmark trials showed consistent survival advantage with intensification of treatment using a combination of ADT, ARIs and chemotherapy early in the disease trajectory. However, despite the robust evidence generated and the guideline recommendations for upfront treatment intensification, real-world data show a strikingly dismal adoption of this strategy. Various factors contribute to this observation including differences in regulatory and reimbursement approvals, resource limitations, as well as lack of biomarkers to guide treatment selection. As more therapeutics are set to join the treatment milieu in mHSPC, increased awareness needs to be generated in the uro-oncology community about this shift in the standards of care, and a call for increased efforts is needed to deliver evidence-based medicine for patients.

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