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PRO AND CON DISCUSSIONS

Systemic treatment of metastatic hormone-sensitive prostate cancer—upfront triplet versus doublet combination therapy

THE CASE FOR FIRST-LINE TRIPLET FOR MHSPC (PROF. BRISTOW)

Annually, >1.2 million new cases of prostate cancer are diagnosed and global prostate cancer-related deaths exceed 350 000 per annum, making it one of the leading causes of cancer-associated death in men.[1] Despite major improvements in the systemic treatment of advanced prostate cancer, metastatic prostate cancer remains an incurable disease with an overall survival (OS) of only 30% at 5 years with an initial diagnosis of metastatic hormone-sensitive prostate cancer (mHSPC).[2] Generally, patients with low-volume disease have a more favourable prognosis than those with high-volume disease. Patients with metachronous metastatic disease, that is patients with metastatic relapse after definitive local treatment, have a better prognosis than patients with *de novo* synchronous metastatic disease.[3] The systemic treatment approaches, however, are so far generally the same.

Current guideline-endorsed treatment options for fit mHSPC (both synchronous and metachronous) comprise lifelong androgen deprivation therapy (ADT) with luteinising hormone-releasing hormone analogue-based, or surgery-based, castration added to either six cycles of docetaxel (DOCE) or an androgen receptor signalling inhibitor [ARSI; e.g. abiraterone acetate plus prednisone (AAP), enzalutamide (ENZA) or apalutamide (APA)].[4] When compared to ADT alone in a randomised setting, these combinations of ADT + DOCE or ADT + ARSI improve OS and other important clinical outcomes including time to castration resistance, pain progression and/or symptomatic skeletal events.[5-7] Such benefits are seen irrespective of the extent of metastatic spread across low- and high-volume patients. For low-volume mHSPC patients, a planned subgroup analysis of the STAMPEDE ARM H study has shown a beneficial impact on OS by irradiating the prostate alone,[8] which has also been adopted as a standard of care (SoC) option in current international guidelines.[4]

Consequently, the question is whether early intensification by combining ADT + DOCE + ARSI would further improve survival of patients with mHSPC. The pivotal phase III trials ARCHES, ENZAMET and TITAN were designed to assess the impact of the addition of either ENZA or APA to ADT for the first-line treatment of mHSPC. In these trials, subsets of patients did receive sequential triplet therapy as DOCE pre-treatment was permitted before randomisation to ARSI or placebo.[9-11] However, none of these triplet therapy secondary analyses showed an improvement of OS, likely due to the low patient numbers within these subgroups.[12]

More recently, two large randomised phase III trials have shown a further significant improvement of OS for upfront triplet combination treatment with the addition of either abiraterone acetate/prednisolone (oral 1000 mg abiraterone OD plus 5 mg prednisone BID) (PEACE-1 trial) or darolutamide (oral 600 mg BID, DARO) (ARASENS trial) in addition to ADT + DOCE (intravenous 75 mg/m2 Q3W, 6 cycles) as SoC.[13,14] The PEACE-1 trial was a phase III randomised controlled trial (RCT) with a 2 × 2 factorial design to assess the impact of the addition of AAP and/or radiotherapy (XRT) to the prostatic primary tumour as additional treatments beyond ADT in patients with synchronous, *de novo* mHSPC.[13] In a first subgroup analysis, 710 patients treated with either ADT + DOCE (an amended new SoC during the trial recruitment phase) or ADT + DOCE + AAP (both arms ± XRT) were assessed. The triplet combination resulted in a 25% reduction of the risk of death [hazard ratio (HR) 0.75; 95% confidence interval (95% CI) 0.59-0.95] with a median OS of 4.4 years for patients receiving ADT + DOCE (±XRT), while median OS in the triplet (±XRT) subgroup had not been reached. In a subgroup analysis stratified by high- or low-volume metastatic disease, the beneficial impact of adding AAP to ADT + DOCE was only seen in patients with high-volume metastatic disease (HR 0.72; 95% CI 0.55-0.95), with a gain of 1.6 years in median OS (3.5 versus 5.1 years). In patients with a low disease volume, results for OS remain inconclusive due to limited follow-up (HR 0.83; 95% CI 0.50-1.39). Time to transition to metastatic castration-resistant prostate cancer (mCRPC) was also significantly longer with the triplet, despite the fact that 81% of patients treated with ADT + DOCE subsequently received ADT + ARSI for mCRPC. The impact of XRT on the prostate has not been analysed so far due to the limited number of survival events for the comparison.

In the ARASENS trial, 1306 mHSPC patients (86% of whom had synchronous, *de novo* metastatic disease) received either ADT + DOCE + placebo or ADT + DOCE + DARO.[14] ARASENS is therefore the only phase III RCT with mandatory application of ADT + DOCE as SoC for all trial participants. Initial triplet treatment reduced the risk of death by 32% (HR 0.68; 95% CI 0.57-0.80), again despite a high proportion of patients in the SoC arm receiving subsequent ARSI treatment upon progression to mCRPC (76%).

The median OS was not reached for the triplet arm and was estimated at 49 months in the SoC arm. Secondary key clinical endpoints, such as time to mCRPC, pain progression and skeletal-related events, were also favouring triplet therapy. Within pre-defined subgroups, a similar effect on OS was seen for both patients with synchronous (HR 0.71; 95% CI 0.59-0.85) and metachronous (HR 0.61; 95% CI 0.35-1.05) mHSPC, with the latter not being statistically significant in this primary analysis. A comparison between both treatments stratified by disease volume, as reported in the PEACE-1 trial, has not yet been reported.

Toxicity profiles in both these phase III studies showed an expected increase of grade $\geq$3 hypertension and liver enzyme elevation with the addition of either ARSI alongside the known haematotoxicity of ADT + DOCE alone. However, there were no increases in overlapping toxicities.

Conclusion

Survival of men with mHSPC has dramatically improved over recent years for the first time exceeding a median of >5 years by adding an ARSI to ADT + DOCE upfront for fit patients with *de novo*, synchronous mHSPC based on PEACE-1 and ARASENS trial data. Since a high proportion of patients treated with first-line ADT + DOCE in both trials received subsequent ARSI treatment for their mCRPC, the upfront intensification seems more effective than a sequential doublet approach starting with ADT + DOCE. The following open questions remain:

(i) Does the optimal management option for patients with low-volume mHSPC (including oligometastatic disease) include short-course prostatic and metastasis-directed XRT in addition to systemic therapy? This is currently being investigated within arm M of the STAMPEDE trial.
(ii) Are there predictive genetic or other biomarkers to individualise treatment intensity and duration decisions?
(iii) What is the best treatment approach for patients with metachronous mHSPC, who were excluded from the PEACE-1 trial and were underrepresented in the ARASENS trial?

Still, with OS as key primary outcome, upfront triplet combination with ADT + DOCE + ARSI will become a new SoC for fit men with *de novo* mHSPC. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) already recommended an extension of the marketing authorisation for DARO now including the indication for men with mHSPC in combination with ADT + DOCE.[15] This will prolong the median life expectancy of *de novo* mHSPC patients beyond the 5-year landmark, which is a remarkable success for this still incurable patient population. Key factors to argue against an initial triplet approach for now seem to be patient fitness and, at least for AAP, a low disease volume based on routine imaging. Future clinical-translational studies are needed to further stratify patients and predict therapy responses in order to prevent tumour evolution and secondary resistance.

THE CASE AGAINST FIRST-LINE TRIPLET FOR MHSPC (DR OING)

With the results of the PEACE-1 and ARASENS studies, for the first time, level 1 evidence supports the use of treatment combinations to achieve a median OS of 5 years or more; this had not been achieved previously in metastatic prostate cancer. Upfront triplet combination therapy seems a promising option for patients with *de novo* mHSPC, especially with high-volume disease ($\geq$4 bone metastases $\pm$ distant lymph node metastases) if they are fit enough to tolerate the increased toxicity.[13,14]

However, upfront triplet therapy is obviously not a one-size-fits-all approach for all mHSPC patients. Given the fact that only ~5% of patients present with synchronous metastatic disease, the majority of mHSPC patients will have had previous radical local treatment for localised disease.[16] Patients with metachronous disease were not included in the PEACE-1 study and were underrepresented in the ARASENS trial. Since patients with metachronous mHSPC have a better prognosis compared to patients with *de novo* mHSPC,[3] they may not benefit from upfront intensified triplet treatment. The same problem stands out for patients with a low metastatic volume, who did not benefit from intensified first-line treatment in a subgroup analysis of the PEACE-1 study, while ARASENS did not report a subgroup analysis based on disease volume.

For patients with metachronous mHSPC and/or low-volume disease, the current SoC will for now remain frontline doublet combination treatment with ADT + DOCE or ADT + ARSI as mentioned in current guidelines, including the European Society for Medical Oncology (ESMO) clinical practice guideline.[4]

The majority of patients with mHSPC respond to therapeutic androgen suppression by surgical or medical castration. However, virtually all patients progress to castration-resistant disease (CRPC) after ~3 years.[7,17,18] The intensification of first-line systemic treatment of mHSPC by adding a second-generation ARSI (e.g. AAP,[5,19] ENZ[9,20] or APA[11]) until radiographic disease progression, or chemotherapy with six cycles of DOCE[7,17,18] substantially improved patient survival and other key clinical outcomes, i.e. time to CRPC, symptom control and deferral of skeletal-related events. To identify the best treatment option, it is critical to explore some details of the two different options, ADT + DOCE and ADT + ARSI, in four different clinical scenarios, e.g. synchronous versus metachronous metastatic disease referred to as patients either presenting or relapsing with metastatic disease and low- versus high-volume metastatic disease defined by the extent of metastatic spread. Patients with synchronous high-volume disease have the most unfavourable prognosis (median OS 43.2 months; 95% CI 37.2-56.6 months), whereas patients relapsing with a low volume after previous local therapy show the best outcomes (median OS 92.4 months; 95% CI 80.4-127.2 months).[3]

Differential cancer biology may well be the most prominent reason for the discrepant survival outcomes; to date, no molecular biomarkers have been identified to allow for more distinguished outcome prediction and better selection for the available treatment options.

First-line chemotherapy for mHSPC

Three large RCTs compared the combination of ADT + six cycles of three-weekly DOCE to ADT alone: GETUG-AFU 15,[17] CHAARTED[7] and STAMPEDE.[18] In terms of OS, adding six cycles of DOCE to ADT prolonged OS by ~5-15 months to a median of almost 60 months.[7,18] Common side-effects include neutropenia with the risk of febrile neutropenia, abnormal liver function tests, fatigue and polyneuropathy.

According to a trial meta-analysis of the three trials with 2261 mHSPC patients, ADT + DOCE did not improve OS for men with metachronous low-volume disease (HR 0.98; 95% CI 0.67-1.45). The biggest reduction of the risk of death and thus OS benefit, instead, was noted among patients with synchronous high-volume disease (HR 0.60; 95% CI 0.52-0.69). Consequently, metachronous low-volume disease demands a different approach for systemic therapy.

First-line ARSI for mHSPC

The alternative to first-line chemotherapy is the use of second-generation ARSIs. Five large RCTs assessed treatment with ADT ± either AAP (LATITUDE, STAMPEDE), ENZ (ENZAMET, ARCHES) or APA (TITAN). In terms of OS, adding an ARSI to ADT significantly improved OS with a reduction in the risk of deaths of ~35% versus ADT alone. Most prominent side-effects are hypertension and hepatotoxicity as a class effect of all ARSIs. Interestingly, the impact of disease burden on treatment efficacy is inconclusive among the different studies likely owing to differences in the study populations. Of the assessed ARSIs in mHSPC, AAP was so far the only drug for which a similar activity for patients with low- and high-volume disease was reported in a subgroup analysis of the STAMPEDE trial.[21]

How to choose between ADT + DOCE and ADT + ARSI

To date, there is no level 1 evidence from a randomised comparison between the two first-line combination options for mHSPC. But, a direct comparison between two treatment arms of the STAMPEDE study, which recruited simultaneously to ADT + DOCE or ADT + AAP, provides important insights to inform treatment choices. In terms of treatment activity and toxicity, there was neither a difference in OS (HR 1.16; 95% CI 0.82-1.65) or prostate cancer-specific survival (HR 1.02; 95% CI 0.70-1.49) nor in the emergence of higher-grade (≥3) treatment-related side-effects, but with the expected differences in the toxicity profiles.[6] Regarding patient-reported outcomes, QoL was better with AAP + ADT compared with DOCE + ADT with clinically meaningful higher global QoL scores throughout the first year. QoL seemed to be negatively impacted during the course of chemotherapy, but improved thereafter.[22] Similar findings were reported for a meta-analysis including data from the CHAARTED, GETUG-AFU 15 and LATITUDE trials.[23] Strikingly, the overall risk reduction of death seemed clearly higher (33%-39%) when an ARSI was added to ADT than with the addition of DOCE (19%-28%) across the above-mentioned studies.

Conclusion

For fit and younger patients with synchronous mHSPC, upfront triplet combination treatment has defined a new benchmark in terms of survival benefit that comes at the cost of increased toxicity. If a triplet is not feasible, both ADT + DOCE and ADT + ARSI are generally equally effective, safe and well-manageable options for first-line mHSPC treatment. The decision for one or another option should be taken based on disease volume, timing of metastasis, patient's performance status and preferences as well as expected intolerabilities based on comorbidities and impact on QoL. Regarding disease burden, patients with a high extent of metastatic spread benefit from both options, and patients with low-volume disease should rather be offered an ARSI, of which most convincing data are available for the combination of AAP + ADT.

JOINT COMMENT ON UPFRONT TRIPLET THERAPY IN THE FIRST-LINE TREATMENT FOR MHSPC (DRS BRISTOW AND OING)

We unanimously agree that the results from PEACE-1 and ARASENS will change the treatment landscape of mHSPC by defining a highly effective treatment approach for fit patients with synchronous, high-volume disease. This obviously reflects a highly aggressive form of prostate cancer with a median OS of ~3 years with doublet combination systemic treatment.[3] Generally, the metastatic setting and patient characteristics obviously guide the decision towards a triplet or doublet combination for now, as outlined previously. Consequently, it seems worthwhile to jointly reflect on the overall treatment landscape of mHSPC and highlight some pivotal questions, which so far remain unanswered, rather than to argument for or against upfront triplet combination therapy. Answering those questions will help further improve outcomes for both, the most unfavourable group of patients with *de novo* high-volume mHSPC and patients with likely less aggressive metachronous and/or low-volume mHSPC.

What is the best treatment approach for patients with metachronous and/or low-volume or oligometastatic disease?

Until today, doublet combination therapy with ADT + ARSI is the established SoC for all patients with metachronous mHSPC (irrespective of disease burden).[4] There is evidence from the STAMPEDE study (arm H) that radiotherapy to the prostatic primary added to SoC (only 17% of patients received ADT + DOCE) improves OS in patients with

synchronous low-volume mHPSC.[8] An updated report confirms that short-course XRT improves OS with excellent QoL in low-volume mHSPC,[24] which is important given it is relatively inexpensive and a broadly available therapeutic across the world. The PEACE-1 study will tell whether or not this holds true with more intensified first-line systemic treatment. Additionally, stereotactic radiotherapy is also under investigation to ablate metastatic sites in oligometastatic (omHSPC) patients ($\leq$3-5 bone metastases $\pm$ lymph node metastases).[25] Two randomised studies showed that local ablation of a limited number of metastatic deposits in patients with metachronous omHSPC defers disease progression to a polymetastatic state thereby deferring the need for systemic mHSPC treatment.[26] However, no prospective evidence is available so far for patients with *de novo* omHSPC. Consequently, omHSPC patients should preferably be treated within clinical trials whenever possible to uniformly define omHSPC and to optimise patient selection criteria based on functional imaging and molecular markers before metastasis-directed therapy may be adopted as SoC.

Are there biomarkers reflecting the biology of the disease to guide us towards more tailored, biology-driven treatment approaches?

To date, molecular biomarkers for response and toxicity prediction and treatment choice remain largely elusive. However, the GAP6 consortium recently identified predictive genomic markers looking into the different settings of mHSPC. Polymetastatic HSPC more frequently harbours high-risk genomic aberrations affecting *TP53* and WNT pathway and cell cycle regulator genes, while driver mutations were found less frequently in samples of patients with biochemical recurrence or oligometastatic recurrence.[27] Patients with low-volume mHSPC with a *TP53* mutation experience more aggressive courses quite similar to high-volume disease.[28] Another genomic analysis of patients with metachronous omHSPC, who were treated within the ORIOLE or STOMP study, showed that patients harbouring high-risk mutations in the *TP53, RB1*, *BRCA1/2* or *ATM* genes derived less benefit from metastasis-directed treatment in order to delay disease progression and the need for subsequent systemic treatment.[26] The only established molecular biomarker for treatment selection are mutations of *BRCA1* or *BRCA2*, which are known to confer a substantially poor prognosis but also provide the option of a targeted treatment with poly (ADP-ribose) polymerase inhibitors such as olaparib for mCRPC.[29,30] However, homologous recombination repair defects based on other genomic abnormalities, such as germline *PALB2* mutations, do not have access to this possibly effective treatment approach.[31] Thus, there is a potential for molecular biomarkers to add to prognostication and response prediction but the aforementioned drivers of aggressive HSPC remain non-targetable, so far. The trend towards treatment intensification so far neglects such features as it solely relies on routine imaging and clinical characteristics.

Who is a suitable candidate for triplet systemic therapy in the real-world setting and does ethnicity impact the tolerability and efficacy of new treatment regimens?

Until today, there are no reliable molecular biomarkers to allow for idiosyncratic individual patient selection for either triplet or doublet first-line combination treatment. The only key factors to guide this decision so far will be the timing of metastasis detection and patient-specific factors, e.g. patient age and comorbidities.

Ethnicity has so far been insufficiently addressed in the treatment of metastatic prostate cancer, but it may well play a substantial role when it comes to prediction and prevention of toxicity and assessment of efficacy. For instance, attenuated DOCE regimens were reportedly less toxic but equally effective in Asian mCRPC patients.[32,33] Pharmacogenomic analyses and ethnicity-focused pharmacokinetic analyses will help shed light on this issue and help to tailor best possible treatment based on patient-specific dosing schedules, which will finally improve treatment tolerability. Then, the question at what point toxicity will matter to accept or avoid side-effects imminent with a triplet combination might lapse. Moreover, a better understanding of genetic differences underlying the disease is needed as, for instance, men of African origin are known to develop more aggressive prostate cancers, but are at the same time underrepresented in clinical trials and suffer from the disparity in the current availability of treatment options within low- to middle-income countries.[34]

In general, there is a need for a better understanding of the principles of clonal evolution and the molecular features of the different metastatic disease scenarios and between different ethnic groups in order to understand prostate cancer as an evolutionary process. This approach will help to identify novel treatment targets and novel concepts of synthetic lethality for future biology-driven trial design and individually tailored treatments with enhanced activity and attenuated toxicity. Only those hold promise to further improve treatment outcomes and help limit overtreatment and unnecessary treatment-related toxicity. Furthermore, implementation of novel response criteria other than prostate-specific antigen and conventional imaging (e.g. based on circulating tumour cells and circulating tumour DNA) may help to guide treatment choices in terms of suitable regimens and their intensity or duration. Altogether, new predictive assays in this clinical setting should focus on tumour and toxicity responses and individual management in patients with comorbidities or differential ethnicity to choose the most effective prostate cancer treatments.

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