Association between Age and Efficacy of Combination Systemic Therapies in Patients with Metastatic Hormone-Sensitive Prostate Cancer: A Systematic review and Meta-analysis

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Abstract

Background: Combination systemic therapies have become the standard for metastatic hormone-sensitive prostate cancer (mHSPC). However, the effect of age on oncologic outcomes remains unknown. Our aim was to perform a systematic review, meta-analysis, and network meta-analysis (NMA) on the effect of chronological age on overall survival (OS) in patients treated with combination therapies for mHSPC.

Methods: We searched the PubMed®, Web of Science™, and Scopus® databases to identify randomized controlled trials (RCTs) that analyzed the efficacy of combination systemic therapies using ADT plus docetaxel and/or androgen receptor signaling inhibitor (ARSI) in patients with mHSPC. We included studies, which provided separate hazard ratios (HRs) for younger vs. older patients. The selected age cut-off was 70 years (+/- 5 years). Our outcome of interest was OS.

Results: We included nine RCTs with a total of 9,183 patients. Younger and older men constituted 51% and 49% of included patients, respectively. Docetaxel plus ADT significantly improved OS among both older (HR 0.79, 95% CI 0.63-0.99, p=0.04) and younger patients (HR 0.79, 95% CI 0.69-0.90, p<0.001) with no differences according to age. ARSI plus ADT improved OS in older (HR 0.72, 95% CI 0.64-0.80, p<0.001) and younger (HR 0.58, 95% CI 0.51-0.66, p<0.001) patients; younger patients did benefit more (p=0.02). On NMA treatment ranking, triplet therapy showed the highest probability of OS benefit irrespective of age group; in older patients, the benefit of triplet therapy compared to doublet was less expressed.

Conclusions: Patients with mHSPC benefit from combination systemic therapies irrespective of age; the effect is, however, more evident in younger patients. Chronological age alone seems not to be a selection criteria for the administration of combination systemic therapies.

Introduction

Up to 7-10% of patients with prostate cancers (PCa) are diagnosed with metastatic disease at presentation, and up to 45% of patients with the primary unfavorable localized disease will eventually develop metastases within 10 years [1-3]. Until recently, androgen-deprivation monotherapy (ADT), which allowed to delay the disease progression, was the standard treatment option for patients with hormone-sensitive metastatic disease (mHSPC) [2, 4]. However, generally after 2 to 3 years of ADT most mHSPC patients progress to the castration-resistant status with a subsequent median survival of approximately 1.5 years [5].

The management of mHSPC has rapidly evolved in recent years; the addition of docetaxel, abiraterone acetate, enzalutamide, or apalutamide to ADT has been proven to prolong survival from 33-35 to 40-61 months [6-14]. Recent meta-analyses found that doublet combination therapies improve oncologic outcomes with comparable efficacy [15]. Moreover, phase 3 randomized controlled trials (RCTs) have shown that, in selected patients, triplet combination therapies may further improve survival [6, 15, 16].

To choose the right therapy for the right patient at the right time, one needs to tailor the treatment intensity to balance the risk of over-and undertreatment, while maintaining quality of life. In this context, older patients typically suffer from other comorbidities and may have lower life expectancy that may compromise the benefit of combination therapies [17, 18]. Overall, high-grade adverse events affect 25-63% of men receiving combination therapies; the risk may be higher for older patients who harbor generally more comorbidities and are often frail [4, 19-21]. On the other hand, over 89% of men who die from PCa are over 65, and older men have worse cancer-specific mortality compared to younger patients [2]. Furthermore, as the population in developed countries is aging, the incidence and morbidity of PCa, which is the most common cancer in elderly men, is increasing. It is expected that in twenty years over two-thirds of newly diagnosed PCa men will be over 70 years of age, and cancer deaths in men aged 70 years will almost double [22, 23]. While most of the recent meta-analyses analyzed oncologic outcomes of combination systemic therapies in the general population, the differential effect of these novel treatment strategies in the elderly men with mHSPC has been poorly addressed so far.

We aimed to perform a systematic review and meta-analysis to assess the impact of chronological age on the efficacy of combination therapies for mHSPC. Furthermore, we conducted a network meta-analysis (NMA) to compare the efficacy of available systemic treatment options within "young" and "older" patients.

2. Material and Methods

2.1. Search strategy

Our study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42022332079). This systematic review and meta-analysis was performed according to PRISMA statement (Supplementary Table 1) [24]. We queried PubMed®, Web of Science™, and Scopus® databases to identify reports published through May 2022, which analyzed the oncologic outcomes in patients treated for mHSPC with combination systemic therapies. Combination systemic therapies must have consisted of ADT plus docetaxel and/or androgen receptor signaling inhibitor (ARSI). Our outcome of interest was OS. The search strategy is provided in Supplementary Table II. The screening was performed by two independent investigators (PR and TY) and was based on titles and abstracts. Full texts were then retrieved and their eligibility was assessed. Any discrepancies were solved by the senior authors.

2.2. Study selection

We found studies eligible if included patients with mHSPC stratified by age groups (population) and compared the efficacy of combination systemic (Interventions) to the efficacy of standard systemic therapies (comparisons). The differential effect of combination therapies among older and younger patients on OS was analyzed (outcome) in RCTs (study design). We included studies, which provided separate hazard ratios (HRs) for younger and older patients. The cut-off for age stratification was 70 years (+/- 5 years, depending on the threshold provided in the RCTs). We excluded meta-analyses, reviews, letters, conference abstracts, case reports, and non-English articles. References of all included reports were screened for additional studies of interest.

2.3. Data extraction

Two authors independently extracted RCTs' data, such as first author names, publication date, combination therapy type, percentage of de novo mHSPC at baseline, mHSPC volume, age, age cut-offs, the total number of patients, and the number of events of interest. Furthermore, we retrieved HRs and 95% confidence intervals (CIs) for OS and oncologic outcomes in older and younger patients treated with combination systemic therapies.

2.4 Risk of bias assessment

In line with the Cochrane Handbook for Systematic Reviews of Interventions risk-of-bias tool (RoB version 2) two investigators independently analyzed the risk of bias (RoB) [25]. Review Manager 5.3 Software (RevMan; The Cochrane Collaboration, Oxford, UK) was used to create RoB figures

2.5. Statistical analysis

2.5.1 Meta-analysis

Forest plots were used to depict and calculate pooled HRs of the effects of combination therapy on survival outcomes in older and younger patients. We performed separate analyses among studies

analyzing chemohormonal therapy (ADT plus docetaxel) and ARSI (ADT plus abiraterone acetate or enzalutamide or apalutamide or darolumatide). Subsequently, we used Meta-ANOVA and t-test to compare pooled HRs between older and younger patients. In our calculations of pooled HRs, we used fixed-effect models. We assessed the heterogeneity in treatment effects between RCTs using Cochrane Q test. In cases of heterogeneity (Cochrane Q test $p < 0.05$), we attempted to investigate and explain the heterogeneity. All the analyses were carried out using R v4.2 (R Foundation for Statistical Computing, Vienna, Austria). We set the statistical significance at $p < 0.05$.

2.5.2 Network meta-analysis

We performed a NMA for OS using random models with a frequentist approach to compare directly and indirectly combination therapies among older and younger patients separately [26, 27]. Network plots were utilized to show the connectivity of the treatment networks concerning OS. For OS appraisal, we used contrast-based calculations with differences in the log HR and the standard error derived from the extracted HR and 95%CI [28]. The relative ranking of the combination therapies' efficacy in older and younger patients was estimated using the surface under the cumulative ranking (SUCRA) [26]. If more than one trial was available for a given comparison, we assessed the heterogeneity using the Cochrane Q test.

3. Results

3.1. Study selection and characteristics

Figure 1 depicts the PRISMA flowchart diagram. After screening and study selection, we included nine RCTs (Tables I and II), yielding a total of 9,183 men treated for mHSPC. Three RCTs analyzed doublet combination therapies using docetaxel plus ADT, five analyzed ARSI plus ADT, and one analyzed triplet combination therapy with ARSI plus docetaxel plus ADT (Table I). Between 58 to 100% of patients treated with combination therapies had primary mHSPC. The median follow-up ranged from 22.9 to 83.9 months. Of note, PEACE-1 [16] trial did not provide separate OS data for younger and older patients and was not included in the present study.

3.1.1. Impact of age on treatment outcome

In the included RCTs the median age ranged from 63 to 70 years. Five trials set their cut-off for age stratification at 70 years, and four at 65 years. Additionally, three studies provided additional HRs data for patients aged 75 years or older (Table II). When restricting to studies that provided absolute numbers of patients for different age groups, younger and older patients constituted 51% and 49% of the overall cohorts, respectively.

For younger patients (using cut-off of 65-70 years), all, but one [14] RCTs (89%) showed a significant association between combination therapies and OS. For older patients a total of five out of

nine RCTs (56%) showed improved OS for combination therapies. In detail, for older patients significant results were found in one study analyzing the impact of docetaxel plus ADT (33% of all docetaxel-based combination therapies), three using ARSI plus ADT (60% of all ARSI-based combination therapies), and one using triplet therapy. In a subgroup analysis of patients aged ≥75 years old, only one RCT (33% of all available) reported a significant impact of combination therapies on OS, however, this can be also attributed to a lower number of events and patients in this smaller group of patients.

3.1.3. Risk of bias assessment

Supplementary Figures 1 and 2 show the summary of the risk of bias (RoB) and applicability concerns, and authors' judgments about each domain for each included study, respectively. Due to their design (prospective RCTs), the included studies had an overall low risk of RoB.

3.2. Meta-analysis

3.2.1. Effect of chemohormonal combination therapies stratified by age

Three studies including 2,261 patients compared the addition of docetaxel to ADT in older (78%) vs. younger (22%) patients with mHSPC. The forest plots (Fig. 2) revealed that among both, older (HR 0.79, 95% CI 0.63-0.99, p=0.04) and younger (HR 0.79, 95% CI 0.69-0.90, p<0.001) patients, docetaxel plus ADT was associated with significantly improved OS. There was no significant difference between younger and older patients. The Cochrane's Q tests (p >0.05) indicated no significant heterogeneity for all calculations.

3.2.2. Effect of ARSI plus ADT stratified by age

Five studies including 5,616 patients analyzed the effect of combination therapy using ARSI and ADT in older (55%) vs. younger (45%) patients with mHSPC. The forest plots (Fig. 3) show that in both older (HR 0.72, 95% CI 0.64-0.80, p<0.001) and younger (HR 0.58, 95% CI 0.51-0.66, p<0.001) patients, doublet therapy with ARSI plus ADT was associated with significantly improved OS. However, there was a significant difference in efficacy between younger and older patients (p=0.02). The Cochrane's Q tests (p >0.05) indicated no significant heterogeneity.

3.2.3. Triplet therapy stratified by age

Only the ARASENS trial provided data on the comparison of triplet vs. doublet combination therapies in younger (37%) and older (63%) patients. As older patients were divided into three categories (Table II), we calculated the pooled HRs to obtain summary data for the subgroup of ≥65-year-olds. Compared to doublet using docetaxel plus ADT, tiplet therapy with darolutamide, docetaxel and ADT improved OS in both, older (HR 0.75, 95% CI 0.60-0.93, p=0.01) and younger (0.59, 95% CI 0.45-0.79, p<0.001) patients. There was no significant difference between younger and older patients (p=0.19).

3.3. Network Meta-analysis

We carried out a NMA for OS to compare ADT plus docetaxel and/or ARSI, with ADT alone or ADT plus docetaxel as common comparator arm (Supplementary Figure 3). Forest plot (Figure 4) shows that among older patients, ARSI and triplet combinations outperformed ADT; for docetaxel plus ADT there was some evidence of improved OS, but it did not meet the level set for the significance (HR 0.78, 95% CI 0.61-1.01, p=0.057). Compared to docetaxel plus ADT (Figure 4), none of the ARSI-based combinations was significantly superior; for triplet therapy despite some evidence, the effect was not significant (HR 0.75, 95% CI, 0.56-1.01, p=0.058). The SUCRA treatment ranking (Supplementary Figure 4) estimated that there was 89%, 71%, 55%, 47%, 37%, and 2% probability that darolutamide plus docetaxel plus ADT, apalutamide plus ADT, enzalutamide plus ADT, abiraterone plus ADT, docetaxel plus ADT, and ADT are the preferred treatments in terms of OS, respectively. There was no significant heterogeneity in the NMA for both, older and younger patients (Cohrane Q test >0.05).

Among younger patients the forest plots show (Figure 4) all combination therapies improved OS compared to ADT. The triplet therapy with darolutamide plus docetaxel plus ADT significantly outperformed doublet therapy using docetaxel (HR 0.59, 95%CI 0.45-0.78); this was also true for abiraterone plus ADT (HR 0.72, 95% CI 0.58-0.90) and enzalutamide plus ADT (HR 0.72, 95% CI 0.53-0.98). There were no other significant differences between treatment agents. On SUCRA treatment ranking (Supplementary Figure 4), there was 90%, 70%, 65%, 54%, 22%, and 0% probability that combination therapy using darolutamide plus docetaxel plus ADT, enzalutamide plus ADT, abiraterone plus ADT, apalutamide plus ADT, docetaxel plus ADT, and ADT alone were the preferred agents.

4. Discussion

We analyzed the association between chronological age and OS outcomes in patients treated with combination therapies for mHSPC. While previous meta-analyses and NMAs focused on overall populations showing no to minimal difference in oncologic outcomes for different available combinations [29], our paper sheds lights on oncologic outcomes in older vs. young patients. Considering the overall trend towards treatment intensification of therapy for unfavorable PCa [29, 30], our results may help in pre-treatment counseling in specific patients' age groups.

There are several clinical implications from our results. First, patients with mHSPC benefit from both ARSI- and docetaxel-based combination therapies compared to ADT irrespective of chronological age. In other words, even in the elderly ADT alone is inferior to ADT plus ARSI and/or docetaxel. Second, while docetaxel plus ADT shows similar efficacy among younger and older patients, ARSI-based combinations overall showed more favorable estimates in younger patients. Third, based on NMA results, triplet therapy followed by doublet using ARSI plus ADT showed the highest probability of the best treatment in terms of OS in both younger and older patients. Fourth, in older patients, the benefit of triple therapy compared to doublet was less evident.

Our pooled results demonstrate that there was no age-related difference in response to the docetaxel-based combination therapies (21% reduced risk of death in both age groups), even though, only one study reported a significant association between ADT plus docetaxel in older patients. Our finding is of high clinical relevance as in daily routine, chemotherapy is often underutilized in elderly [19, 31, 32]. This can be attributed to the fear of worse tolerability and excepted lower survival benefits in older men, i.e. fear of overtreatment and decrease in health quality of life [19, 31, 32]. In a study by Lange et al., a posthoc analysis of CHAARTED trial, older patients had comparable rates of high grade (grade ≥3) events compared to younger patients (37% vs. 27%, p = 0.07); the efficacy was similar across age groups [19]. Notably, patients who received all planned docetaxel cycles lived significantly longer (32.7 months vs. 23.5 months, p<0.001) [19]. On the other hand, a Canadian real-world population-based cohort study including also mHSPC patients demonstrated that in elderly patients (>65 yrs), docetaxel-based chemotherapy was associated with a worse safety profile than reported in clinical trials [32]. Furthermore, we still have sparse data in very old patients; based on our results the evidence for patients 75 yrs or older is weaker. It is also important to note that older patients are less likely to be enrolled in clinical trials, and those enrolled have in general better performance status and lower comorbidity index than the general population [33]. Indeed, most of the analyzed RTCs did not include patients with ECOG 2 or included only a very small proportion of these patients; the majority of the included were ECOG 0. Therefore, in real-life scenarios, older patients may still benefit from pre-chemo geriatric oncology assessment using for example G-8 screening tool [34].

We found that ARSI-based combination therapies were highly effective in both age groups. However, more favorable efficacy was observed in younger patients. While the reason for this effect remains unexplored and mostly hypothesis-generating is important to consider the competing causes of death, drug interactions, and overall different drug pharmacokinetics among older patients [21, 35, 36]. A recent US Food and Drug Administration pooled analysis of three randomized trials analyzing the effect of ARSI in non-metastatic castration-resistant prostate cancer (CRPC) showed that significant OS benefit among older (≥80 yrs; HR 0.79 [95%CI 0.64-0.98]) and younger (<80 yrs; HR 0.69 [95%CI 0.60-0.80]) patients [37]. Older patients treated with ARSI plus ADT were at approximately 20% higher risk of grade ≥3 AEs compared to younger men (55% vs. 44%, respectively) [37]. Moreover, recently, the ACIS trial which had evaluated the role of ARSI combination in metastatic CRPC has highlighted a higher survival benefit in the combination treatment arm for older patients, suggesting that chronological age should not be considered as a strict contraindication factor to reinforced systemic therapy [38]. Previous studies revealed overall a good patients' adherence to ARSI [30], also among older patients [39, 40]. Furthermore, post-hoc analyses of ARSI-based trials in CRPC showed that older patients receiving ARSI have a higher risk of falls, fractures, and cardiovascular events [20, 21, 40]. PCa in the elderly seems to have a distinct disease trajectory, and more aggressive pathologic and genomic features, that may lead to a lower response to ARSI [41, 42]. Nevertheless, the 42% and 28% decreased risk of

any cause of death with ADT + ARSI compared to ADT alone in the young and elderly, respectively, translated into all mHSPC patients, without contraindications, should be offered ARSI-based combination therapies.

Our NMA suggests that triplet therapy using ADT plus darolutamide plus docetaxel may be the most preferred combination treatment for patients with mHSPC. However, based on our results, the only clear statistical difference in favor of triplet therapy, with regard to doublet, was compared to docetaxel plus ADT among younger patients; for older patients the effect did not reach conventional level of significance. In younger patients there was also some evidence favoring doublet therapy using abiraterone or enzalutamide over docetaxel plus ADT, which suggests that ARSI-based combinations may have more favorable effect on OS among this population. Again, ARASENS included only patients with ECOG $\leq$1, thus the clinical benefit of triplet therapy among patients with worse performance status is unknown [6]. Furthermore, PEACE-1 trial showed that the effect of triple combination therapy on OS was only significant for patients with high-volume mHSPC, but not low-volume [16]. Therefore, at present, a strong recommendation for the routine use of triplet therapy among different age groups cannot be made and our findings and treatment rankings should be considered as hypothesis-generating.

There are some limitations to our study. First, the included RCTs provided data for younger vs. older patients using the 65-70 years cut-off, therefore the definition of "older" patients varied according to clinical trials. Nonetheless, we should highlight that the use of a single cut-off for defining older patients might be difficult to apply in the clinical practice and that little variations in the definitions of the older category should not affect the generalizability of our results. Second, as previously discussed, RTCs include older patients with favorable performance status, while in the real world, elderly patients with mHSPC often suffer from multiple comorbidities. Third, to the best to our knowledge, PEACE- 1 and SWOG-1216, did not provide efficacy stratified by patient ages, thus we could not include them [16, 43]. Fourth, published RCTs do not provide data that allows for different subgroup comparisons such as low vs high volume, de novo vs pre-treated mHSPC. Fifth, docetaxel plus ADT was given in 45%, 18% and 11% of patients in ENZAMET, ARCHES and TITAN trial. Sixth, the selection criteria for ARSI plus ADT trials were different than those including docetaxel, creating a potential bias. Finally, biological age is not reported in any of the studies and frailty or comorbidity index were not standardly included.

Conclusions

Patients with mHSPC benefit from combination systemic therapies beyond ADT alone irrespective of chronological age. Age should not preclude the administration of combination therapies in this setting. While we did not find any significant impact of age on the efficacy of docetaxel plus ADT, ARSI plus ADT showed higher efficacy among younger patients. Nevertheless, ARSI plus ADT was also more effective than ADT alone in the elderly; the benefit among younger patients was estimated to be a third

larger. Triplet therapy followed by doublet using ARSI plus ADT showed the highest probability of the best treatment in terms of OS in younger and older patients. There is a need for real-world data analyzing patients across the entire performance and frailty. Finally, a net benefit assessment needs to be included to assess intensified PCa systemic therapies in different health status groups to help decision-making regarding the best treatment selection.

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Conflict of interest

PR and GG served as a speaker and/or consultant and/or advisory board for Janssen, SFS has served as a speaker and/or consultant and/or advisory board for Astellas, Astra Zeneca, BMS, Ferring, Ipsen, Jansen, Lilly, MSD, Olympus, Roche, Sanofi, Takeda, and Urogen. CK has received consultant fees from Apogepha, researchfunding from AAA/Novartis and Curie Therapeutics and compensation for travel from Janssen.

Author contribution

Conception and design Rajwa, Shariat, Gandaglia; Acquisition of data Rajwa, Yanagisawa, Shariat, Gandaglia; Analysis and interpretation of data Rajwa, Yanagisawa, Shariat, Gandaglia; Drafting of the manuscript Rajwa, Heidegger, Zattoni, Marra, Soeterik, van den Bergh, Kesch, Ploussard, Shariat, Gandaglia; Critical revision of the manuscript for important intellectual content Valerio, Ceci, Kesch, Kasivisvanathan, Nyiriadi, Trinh, Chlosta, Karakiewicz, Briganti, Montorsi; statistical analysis Rajwa, Kawada

Data availability

All the data used for this study are available online on journal sites where the included studies were retrieved from.

Code availability

Example R code used for this analysis is found in a statistical methodology papers by Shim et al. [26, 44]

Figure 1. PRISMA flowchart

Figure 2. Forest plots show the effect of docetaxel-based combination systemic therapies on overall survival in older and younger patients

Figure 3. Forest plots show the effect of ARSI-based combination systemic therapies on overall survival in older and younger patients

Figure 4. Forest plots show the effect of combination systemic therapies on OS in older (A-B) and younger (C-D) patient with mHSPC: A) ADT as reference B) Docetaxel plus ADT as reference C) ADT as reference B) Docetaxel plus ADT as reference

Table I. Basic characteristics of included RTCs

Table II. Impact of combination therapies stratified by age groups in included RCTs

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Central PMCID: PMCPMC3196245 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare support from the Cochrane Collaboration for the development and evaluation of the tool described; they have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.
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