Treating De novo metastatic castration sensitive prostate cancer with visceral metastases: an evolving issue

Running title: novel androgen-signalling–targeted inhibitors and visceral metastases

Giandomenico Roviello MD PhD[1], Roberto Petrioli MD[2], Donata Villari[3]MD, Alberto D'Angelo MD PhD[4]

1) Department of Health Sciences, University of Florence, viale Pieraccini, 6, 50139, Florence, Italy
2) Medical Oncology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy
3) Department of Urology, University of Florence, Florence, Italy
4) Department of Biology and Biochemistry, University of Bath, Bath BA2 7AY, United Kingdom

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Address for correspondence:
Giandomenico Roviello MD PhD
Department of Health Sciences, University of Florence, viale Pieraccini, 6, 50139, Florence, Italy
E-mail: giandomenicoroviello@hotmail.it

Visceral metastasis is widely considered a prognostic factor for overall survival of men with metastatic castration-sensitive prostate cancer (mCSPC) and has been historically managed with androgen deprivation therapy (ADT). More recently, this therapeutic scenario has been enriched by the possibility to integrate ADT with chemotherapy or novel androgen-signalling–targeted inhibitors. In order to define the effect of chemotherapy/androgen-signalling–targeted inhibitors plus ADT, we performed a pooled analysis on patients with mCSPC and visceral metastases revealing that survival was significantly improved in patients without visceral metastasis (HR=0.64 95%CI: 0.56-0.74; p<0.01) compared with men with visceral metastases (HR=0.68; 95%CI: 0.51-0.91**;** p<0.01). Although several limitations do not allow to draw definitive conclusions, our analysis confirms the efficacy of chemotherapy/androgen-signalling–targeted inhibitors in combination with ADT also in mCSPC with visceral metastases. In the absence of specific randomized controlled trials, symptoms, toxicity, cost, patients' preference and clinical experience should guide the decision to add chemotherapy or androgen receptor-targeted therapy to ADT in patients with visceral metastases from mCSPC.

Introduction

Metastatic castration-sensitive prostate cancer (mCSPC) accounts for lesser than 10% of patients of all new prostate-cancer **[1].** Although mCSPC has been historically managed with androgen deprivation therapy (ADT) through medical or surgical castration, more recently its therapeutic scenario has been enriched by the possibility to integrate ADT with chemotherapy or novel androgen-signalling–targeted inhibitors. From 2015, the addition of docetaxel to ADT for men with high-volume mCSPC has been considered the gold standard **[2]**, as well as abiraterone acetate plus ADT have also improved overall survival in mCSPC **[3,4]**, regardless of the burden of disease **[5].** Similarly, apalutamide and enzalutamide were evaluated with interesting results in different phase III randomized trials **[6-8].** All these studies showed a survival advantage in favour of novel androgen-signalling–targeted inhibitors although there is the need for prognostic factors to better stratify the patients considering that another strategy with a combination of chemotherapy to ADT **[9]** is available, and a direct comparison between all these approaches (docetaxel + ADT vs novel androgen-signalling–targeted inhibitor + ADT) is lacking.

Discussion

Visceral metastasis is widely considered a prognostic factor for overall survival of men with mCSPC. Data from different phase III trial suggest that visceral metastases (mainly lung or liver metastasis) account for less than 20% of patients with mCSPC **[10]**. Treating men with visceral metastases from de-novo' mCSPC is considered an interesting challenge as no study reported a direct comparison from docetaxel + ADT versus novel androgen-signalling–targeted inhibitor plus ADT.

From 2015, the addition of docetaxel to ADT has been investigated in three different phase III trials: the CHAARTED, the GETUG-AFU15 and the STAMPEDE (an arm of docetaxel) trials **[9,11,12].** Docetaxel (Taxotere) is a member of the taxanes family which promotes aggregation of microtubules and the consequent inhibition of microtubule depolymerization tubulin, leading to the M-phase cell-cycle arrest and apoptosis through B-cell lymphoma (Bcl-2) phosphorylation **[13]**. The TAX 327 clinical trial was the first study to report efficacy of docetaxel for prostate cancer patients: in this study, 1006 patients refractory to the hormonal treatment were randomized to receive either docetaxel versus standard of care (SOC) mitoxantrone. Patients administered with docetaxel showed a higher survival rate than those administered with SOC, namely 18.9 months versus 16.5 months respectively (P=0.009) **[14]**. In the recent past, the CHAARTED randomized trial recruited 790 metastatic prostate cancer patients to receive ADT plus docetaxel or ADT alone. Patients with high-volume disease (bone metastasis only) reported a hazard ratio of 0.64 (0.46 – 0.89) while patients with visceral metastasis - observed in the 14% of patients in the experimental arm and 17% of patients in the control arm – reported a significant hazard ratio of 0.52 (0.25 – 1.07). In the GETUG-AFU15 trial, visceral metastases were observed in the 15% of men in the experimental arm and 12% of men in the control arm. However, the hazard ratios observed for GETUG-AFU15 study were 1.06 (0.41 – 2.75) for patients' group with no bone metastasis and 1.01 (0.74 – 1.38) for the patients' group diagnosed with bone metastasis. The STAMPEDE trial, which enrolled fewer patients with visceral metastases - liver metastases and lung metastases were reported in approximately 3% of all patients evaluated - a confirmed hazard ratio of 0.95 (0.62 – 1.47) was observed for patients with no metastatic lesions and a hazard ratio of 0.76 (0.62 – 0.92) for the metastatic patient group.

The efficacy of androgen-signalling–targeted inhibitors plus ADT for patients with visceral metastases has been tested in several studies. The steroids abiraterone acetate (AA) and

prednisone are administered together to inhibit CYP17 and zeroing the synthesis of androgens. Normally, CYP17 promotes the conversion of progesterone and pregnenolone to testosterone precursors; its inhibition leads to the decrease of cortisol levels and the compensatory rise of adrenocorticotropic hormone (ACTH) which, in turn, is hampered by the concomitant administration of steroids **[15]**. The COU-AA-301 study has been a cornerstone for the AA clinical approval: 1195 patients with prostate cancer were randomly assigned to receive either 1000 mg of AA or placebo with a prolonged OS for abiraterone acetate group (14.8 months vs. 10.9 months, HR = 0.65) **[16]**. More recently, the addition of abiraterone acetate and prednisone to ADT in CSPC has been investigated in two large trials: LATITUDE and STAMPEDE (abiraterone acetate arm) **[3,4].** In the LATITUDE trial, where 1199 patients were randomly assigned to receive either ADT plus AA (1000 mg daily) or ADT plus dual placebos, the patients group with no visceral metastasis reported a final hazard ratio of 0.66 (0.53 – 0.82) whereas the patients' group with visceral metastasis - nearly 20% of patients - reported a significant hazard ratio of 0.51 (0.33 – 0.79). Although the total median overall survival (OS) was 32 months in the placebo arm and not reached for the abiraterone arm (**Table 1**), the hazard ratio was in favour of patients with visceral metastases (0.51 versus 0.66).

Enzalutamide has been investigated in two randomized trials for men with mCSPC (ENZAMET and ARCHES) **[6,8]**. Enzalutamide (Xtandi®) is a second-generation androgen receptor (AR) inhibitor which prevents androgen binding to the AR, activated AR nuclear translocation and its binding to the DNA, resulting in significant impairment of the AR signalling pathways at different stages **[17]**. In the first place, enzalutamide showed a meaningful lower risk of metastasis in the phase III PROSPER clinical trial where 1401 non-metastatic prostate cancer patients were randomized 2:1 to receive 160 mg enzalutamide or placebo once daily. The median metastasis-free survival was 36.6 versus 14.7 months among patients administered with enzalutamide and placebo respectively

[18]. In the ENZAMET clinical study, a total of 1125 metastatic hormone-sensitive prostatic adenocarcinoma patients were enrolled. Patients with no metastasis who received enzalutamide benefited the most with a hazard ratio of 0.62 (0.47 – 0.82) whereas among patient with visceral metastasis - about 10% of patients - reported a hazard ratio of 1.05 (0.54 – 2.02). In the ARCHES trial, a total of 1150 men diagnosed with prostate cancer – no patients with visceral metastases – were randomly assigned 1:1 to receive enzalutamide (160 mg/day) or placebo For patients with disease localization at baseline at bone only, soft tissue only and bone plus soft tissue the hazard ratios observed were 0.33 (0.22 – 0.49), 0.42 (0.15 – 1.20) and 0.42 (0.30 – 0.60) respectively **[19]**.

Apalutamide is another novel non-steroidal antiandrogen agent which binds directly to the ligand-binding domain of the AR and, similarly to the enzalutamide, stops the AR translocation, DNA binding and the consequent androgen-receptor-mediated transcription **[20]**. Apalutamide agent firstly showed significant efficacy in the phase III SPARTAN trial where a total of 1207 non-metastatic prostate cancer patients were randomized 2:1 to receive apalutamide or placebo in combination with ADT **[20]**. Patients administered with apalutamide reported statistically significant longer metastasis-free survival (40.5 versus 16.2 months) [HR = 0.28 (95% CI = 0.23-0.35) **[20]**. Afterwards, apalutamide has been tested against standard ADT in the TITAN trial **[7]** where 525 patients were randomly assigned to apalutamide group and 527 to the placebo group. Among the patients' group with only bone metastasis at baseline and no visceral metastasis, the hazard ratio was 0.63 (0.56-0.74). The patients' group with visceral disease and bone metastasis at baseline - about 10% of patients had lung metastases and more than 2% of patients had liver metastases - reached a hazard ratio of 0.99 (0.55–1.77)

In order to define the effect of chemotherapy/androgen-signalling–targeted inhibitors plus ADT, we performed a pooled analysis on patients with mCSPC and visceral metastases

with all available data; therefore, data from LATITUDE, ENZAMET, TITAN and CHAARTED trials were analysed **[3,6,7,9] (Table 1).** A pooled analysis based on the presence of visceral metastasis revealed that survival was significantly improved in patients without visceral metastasis (HR=0.64 95%CI: 0.56-0.74; *p*<0.01 **Figure 1**), as well as men with visceral metastases (HR=0.68; 95%CI: 0.51-0.91**;** *p*<0.01 **Figure 1**).

The presence of visceral metastases in CSPC is generally related to a poor prognosis. It has been estimated that up to 15% of de novo mHSPC patients had visceral metastases at the diagnosis **[13].** Visceral metastases are one of the three criteria to define both high-volume CSPC (used to decide patients to treat with chemotherapy + ADT) and high-risk CSPC (used to decide to treat patients with abiraterone acetate + ADT). Interestingly, although high-volume disease and high-risk disease were mainly used to classify patients in the CHAARTED and LATITUDE studies **[3,9]**, several retrospective studies validated their prognostic role in different populations of mCSPC **[21-23]**. Until 2015, men with visceral metastases from CSPC were treated with ADT alone; in our pooled analysis from literature data, we observed that the HR for survival of patients treated with chemotherapy/novel androgen-signalling–targeted inhibitors + ADT is similar regardless the presence of visceral metastases (patients with visceral metastases HR=0.68; patients without visceral metastasis HR=0.64 **Figure 1**). In fact, the efficacy and safety of docetaxel, as well as the efficacy and safety of novel androgen-signalling–targeted inhibitors, are well described in patients with visceral metastases from prostate cancer **[24-25]**. Based on these data, there is a strong rationale to add chemotherapy/novel androgen-signalling–targeted inhibitors in patients with de-novo metastatic CSPC with visceral metastases. One of the main questions still pending is which approach between chemotherapy and androgen-signalling–targeted inhibitors in addition to standard ADT is better for metastatic mCSPC with visceral metastases. To the best of our knowledge, the

most suitable treatment for these patients remains an evolving issue that requires further investigations in specific studies.

Conclusion

Although several limitations including the low number of studies evaluated, the literature-based approach rather than a patients-based metanalysis do not allow to draw definitive conclusions, our analysis confirm the efficacy the use a novel treatment option in combination with ADT also in mCNPC with visceral metastases. Unfortunately, the best strategy (chemotherapy or AR-targeted therapy) for patients with visceral metastases, currently driven by symptoms, toxicity, cost, patients' preference and clinical experience, still needs to be identified.

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Legends

Figure1. Subgroup analysis for overall survival of chemotherapy/novel androgen-signalling–targeted inhibitor + ADT according to the presence of visceral metastases.

Table 1. Characteristics of the analysed trials and events according to the presence of visceral metastases.

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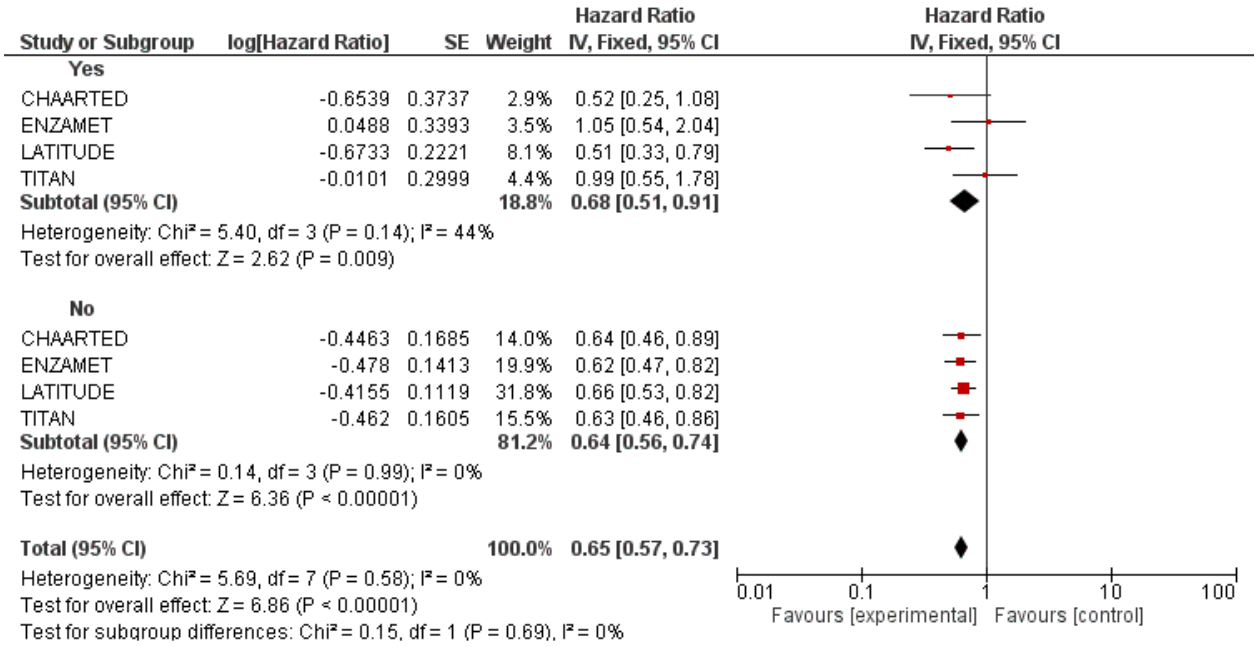
Table 1. Characteristics of the analysed trials and events according to the presence of visceral metastases.

Trial	Drug	Overall survival	
		Number of events /Number of Patients Experimental arm	Number of events /Number of Patients Control arm
Visceral Metastases			
LATITUDE	Abiraterone Acetate	52/114	70/114
ENZAMET	Enzalutamide	18/62	18/67
TITAN°	Apalutamide	20/56	25/72
CHARTEED°°	Docetaxel	NR	NR
No visceral metastases			
LATITUDE	Abiraterone Acetate	223/483	273/488
ENZAMET	Enzalutamide	84/501	125/495
TITAN°	Apalutamide	55/236	64/258
CHARTEED	Docetaxel	NR	NR

° Include men with bone metastasis
°° Visceral metastases with or without bone metastases
NR Not reported

"Number of events Experimental (control) arm" should be "Number of events Experimental /Number of Patients Experimental (control) arm".



Roviello g: Conceptualization, Methodology, Software

Petrioli r.: Data curation, Writing- Original draft preparation.

Villari d: Supervision.:

D’angelo a: Writing- Reviewing and Editing,