Maintenance of androgen deprivation therapy or testosterone supplementation in the management of castration-resistant prostate cancer: that is the question

Irene Caramella1 · Alberto Dalla Volta1 · Marco Bergamini1 · Deborah Cosentini1 · Francesca Valcamonico1 · Alfredo Berruti1

Received: 23 June 2022 / Accepted: 3 August 2022 / Published online: 20 August 2022 © The Author(s) 2022

Abstract

Purpose Whether or not androgen receptor (AR) axis could still be targetable in castration resistant prostate cancer (CRPC) patients with disease progression to next generation hormonal agents (NGHAs) is a controversial issue.

Results Serum testosterone in CRPC patients has a positive prognostic role and increasing testosterone levels after androgen deprivation therapy (ADT) withdrawal or testosterone supplementation, as part of a bipolar androgen therapy (BAT) strategy, has been shown to potentially restore sensitivity to previous lines of NGHAs.

Conclusion These data suggest that maintenance of ADT in CRPC patients receiving further lines of treatment, as recommended by current international guidelines, could be questionable. Conversely, testosterone supplementation aimed to re-sensitize CRPC to further hormonal manipulation is a strategy worth to be explored in future clinical trials.

Keywords Castration resistant prostate cancer · Androgen deprivation therapy · Testosterone · Bipolar androgen therapy

Prostate cancer is an androgen-dependent disease and androgen deprivation therapy (ADT) is the mainstay of treatment for relapsed or metastatic patients. The biology of castration resistant prostate cancer (CRPC) still depends on androgen receptor (AR) signaling through AR gene amplification, overexpression, and production of ligand-independent variants [1]. This implies that patients with CRPC frequently obtain a consistent benefit from the administration of next generation hormonal agents (NGHAs) such as enzalutamide, abiraterone, apalutamide, and darolutamide. Upon progression to these drugs, however, the therapeutic relevance of AR targeting in further disease management seems to be elusive, since retrospective [2] as well as prospective [3] clinical data show that NGHAs in this setting are poorly effective, with an estimated overall response rate of 12–13%.

Recently, on the basis of the results of several prospective randomized clinical trials, that have demonstrated a remarkable efficacy of NGHAs in HSPC patients, the current use of these drugs has moved from CRPC to HSPC setting. So CRPC phenotype has changed and NGHAs will no longer be effective in this context.

Whereas newer treatment strategies are focused on targets beyond the AR (i.e., PARP-inhibitors, radioligands, and immunotherapy), international guidelines still recommend the maintenance of castrate levels of testosterone in pretreated CRPC patients [4]. This recommendation, however, is based on questionable evidence, derived from a single retrospective study showing a modest advantage in overall survival for patients maintaining ADT in association with an outdated chemotherapy regimen [5]. Noteworthy, this survival benefit was not confirmed in 4 subsequent retrospective studies [6–9].

Based on these considerations, is there still a role for castration in CRPC patients receiving AR independent treatments upon progression to NGHAs?

A meta-analysis by Claps et al. [10] showed that the correlation between serum testosterone and prostate cancer
prognosis varies in different clinical settings across the natural history of the disease.

The authors observed an inverse relationship between serum testosterone concentrations and patient prognosis, either in terms of progression-free survival (PFS) or OS, in metastatic HSPC patients after few months of ADT. Conversely, in CRPC patients, higher testosterone levels were associated with longer PFS and OS, regardless of the type of treatment received (NGHAs or docetaxel).

The observed positive prognostic effect of testosterone levels in CRPC patients may question the appropriateness of maintaining ADT in this phase of the disease, mostly when associated with non-hormonal treatments such as chemotherapy.

This issue was addressed in the PON-PC study, a recently published clinical trial where CRPC patients were randomized to receive docetaxel with or without ADT maintenance [11]. The results showed no difference in efficacy outcomes (OS, radiological and biochemical PFS) between the two arms.

Unfortunately, the generalization of the study results was hampered by 2 major limitations: (1) the study was early interrupted when 1/3 of planned patients were enrolled, (2) only 7% of patients randomized to ADT withdrawal achieved a serum testosterone level >0.5 ng/ml in the off-therapy phase, in contrast with the reported time to testosterone normalization of about 3 months in HSPC patients in the off phase of intermittent ADT schedules [12]. Testicular atrophy, due to the long-term ADT exposure in the majority of the PON-PC patients, could be a plausible explanation for this phenomenon [13–15].

These limitations notwithstanding, PON-PC study found that patients randomized to discontinuation of ADT, achieving testosterone levels above the castration range, did not have a worse prognosis than their counterpart. Conversely, a non-significant survival increase of 4 months was observed in this subgroup, in accordance with the results of the meta-analysis by Claps et al. [10].

The results of the PON-PC trial clearly demonstrate that most CRPC patients do not undergo complete testosterone restoration upon ADT withdrawal alone, suggesting that a testosterone replacement therapy is required [16].

Indeed, efficacy and safety of testosterone supplementation in CRPC setting were investigated in studies exploring the so-called bipolar androgen therapy (BAT).

BAT is a therapeutic strategy based on periodic administration of injective testosterone in combination with ADT [17]. The resulting alternative supraphysiological and near-castrate hormonal concentrations exert an antiproliferative activity through impaired regulation of AR expression in response to hormonal fluctuations and subsequent disruption of DNA relicensing required for cell division [18]. BAT, as a single antineoplastic therapy, demonstrated a clinically significant activity both in terms of PSA response and disease control in four single-arm phase I/II studies involving pre-treated CRPC patients [19].

The first randomized clinical trial with BAT (TRANSFORMER), recently published by Denmeade et al., compared BAT with enzalutamide in CRPC patients progressing on abiraterone and showed similar efficacy outcomes for the two apparently opposed therapeutic strategies [20]. Of note, health-related quality of life (HRQoL) and patients reported outcomes (PROs) significantly favored BAT compared to enzalutamide, hinting at a potential clinical benefit of testosterone restoration in terms of fatigue, sexual dysfunction and eventually other hypogonadism-related metabolic toxicities [21–23].

These data are in line with previously cited phase I/II studies and clearly show that testosterone can be safely administered to CRPC patients, with the potential to achieve disease response and a consistent improvement in HRQoL.

Back to PON-PC trial, another relevant phenomenon was observed in patients experiencing hormonal restoration: 4 study subjects, whose testosterone serum concentrations reached normal levels upon luteinizing hormone-releasing hormone agonist (LHRHa) withdrawal, were described to achieve durable disease control with ADT resumption as the only active agent in further line of treatment [24]. In detail, three out of four patients showed a 50% PSA decrease and in one case a radiological response was reported. The disease control duration to LHRH-A re-introduction in this small series was 4, 9, 14 and 28 months, respectively.

This original, though anecdotal, observation suggests that testosterone recovery could restore sensitivity to previous AR targeted therapies. As a matter of fact, three among the aforementioned non-randomized studies reported on the efficacy results of enzalutamide and abiraterone rechallenge upon progression to BAT and observed a PSA response ranging from 16 to 88%, and a PFS ranging from 4 to 6 months [19].

Furthermore, in the TRANSFORMER trial about 40% of patients randomized to BAT vs enzalutamide crossed over to the alternative treatment at progression, allowing an explorative comparison between the two different sequences. Interestingly, patients who received the treatment sequence of BAT followed by enzalutamide had significantly longer cumulative PFS than the opposite sequence (28.2 vs 19.6 months).

A comprehensive list of published data reporting the efficacy of ADT/NGHA rechallenge after testosterone restoration is depicted in Table 1.

Ongoing studies are testing the association between BAT and chemotherapy (carboplatin, NCT03522064), immunotherapy (nivolumab, NCT03554317) and PARP-inhibitors (olaparib, NCT03516812).

The biological rationale of combo therapies is based on the acknowledgement that rapidly fluctuating testosterone
levels may cause DNA breaks and genomic instability, a condition that can be exploited by treatments targeting DNA or neoantigens [25]. Preliminary results of BAT plus nivolumab/olaparib phase II trials have been recently presented, with encouraging PSA50 rate of 40–47% in similar CRPC pre-treated patient populations [26, 27]. Of note, in the olaparib combination PSA response as well as objective response were independent from DNA damage repair gene mutational status, suggesting a synergistic activity of BAT with PARP inhibition.

These data deserve to be validated within randomized phase III trials aimed at finding the optimal setting (first vs further treatment lines), schedule (intermittent vs continuous) and possible companion drug for testosterone administration in CRPC patients.

In conclusion, evidence suggests that serum testosterone has a positive prognostic role in CRPC, so ADT maintenance in CRPC patients receiving concomitant AR independent therapies is questionable. Indeed, the observation of a successful rechallenge with hormonal agents after a transient restoration in testosterone levels claims for the possibility to expand efficacy of AR-targeted therapies in CRPC setting, with relevant implications for clinical practice since these agents are currently being used in the early management of hormone-sensitive disease. In order to achieve rapid testosterone recovery in CRPC patients, ADT discontinuation alone is not sufficient and hormonal replacement is required.

Testosterone can positively influence the patients’ quality of life, which is a key clinical endpoint in late CRPC. Whether testosterone supplementation, in association with active antineoplastic therapies for patients with CRPC, should be administered continuously to achieve stable testosterone levels within normal limits or follow the BAT schedule is a matter for future research.

**Author contributions** A.D., I.C.: conceptualization, manuscript writing. M.B.: manuscript writing. D.C., F.V.: manuscript editing. A.B.: supervision conceptualization, manuscript editing.
Funding A. Berruti and A. Dalla Volta disclose research funding from: Astellas, Ipsen, Janssen. Open access funding provided by Università degli Studi di Brescia within the CRUI-CARE Agreement.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

References

1. A. Berruti, A. Dalla Volta, Resistance to hormonal therapy in prostate cancer. Handb. Exp. Pharm. 249, 181–194 (2018). https://doi.org/10.1007/164_2017_21

2. O. Caffo, U. De Giorgi, L. Fratino et al. clinical outcomes of castration-resistant prostate cancer treatments administered as third or fourth line following failure of docetaxel and other second-line treatment: results of an Italian Multicentre Study. Eur. Urol. 68, 147–153 (2015). https://doi.org/10.1016/j.eururo.2014.10.014

3. R. de Wit, J. de Bono, C.N. Sternberg et al. Cabazitaxel versus Abiraterone or Enzalutamide in metastatic prostate cancer. N. Engl. J. Med. 381(26), 2506–2518 (2019). https://doi.org/10.1056/NEJMoa1911206

4. P. Cornford, R.C.N. van den Bergh, E. Briers et al. EAU-ENAM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of relapsing and metastatic prostate cancer. Eur. Urol. 50302-2838(20), 30773–30779 (2020)

5. C.D. Taylor, P. Elson, D.L. Trump, Importance of continued testicular suppression in hormone-refractory prostate cancer. J. Clin. Oncol. 11, 2167–2172 (1993)

6. M. Hussain, M. Wolf, E. Marshall et al. Effects of continued androgen-deprivation therapy and other prognostic factors on response and survival in phase II chemotherapy trials for hormone-refractory prostate cancer: a Southwest Oncology Group report. J. Clin. Oncol. 12(9), 1866–1875 (1994).

7. J.L. Lee, J. Eun Kim, J.H. Ahn et al. Role of androgen deprivation treatment in patients with castration-resistant prostate cancer, receiving docetaxel-based chemotherapy. Am. J. Clin. Oncol. 34(2), 140–144 (2011).

8. Dong Hoon Lee, Jung Ho Kim, Won Ik Seo et al. Clinical Outcomes of continuous addition of androgen deprivation therapy during docetaxel chemotherapy for patients with castration-resistant prostate cancer. J. Urol. Oncol. 15(2), 59–65 (2017)

9. K. Min, J.W. Chang, Y.S. Ha et al. Efficacy of androgen deprivation therapy in patients with metastatic castration-resistant prostate cancer receiving docetaxel-based chemotherapy. World J. Mens. Heal. 38(2), 226–235 (2020)

10. M. Claps, F. Petrelli, O. Caffo et al. Testosterone levels and prostate cancer prognosis: systematic review and meta-analysis. Clin. Genitourin. Cancer 16(3), 165–175.e2 (2018). https://doi.org/10.1016/j.clgc.2018.01.005

11. S. Bianchi, A. Mosca, A. Dalla Volta et al. Maintenance versus discontinuation of androgen deprivation therapy during continuous or intermittent docetaxel administration in castration-resistant prostate cancer patients: A multicentre, randomised Phase III study by the Piemonte Oncology Network. Eur. J. Cancer 155, 127–135 (2021). https://doi.org/10.1016/j.ejca.2021.06.034

12. K.F. Kuo, R. Hunter-Merrill, R. Gulati et al. Relationships between times to testosterone and prostate-specific antigen rises during the first off-treatment interval of intermittent androgen deprivation are prognostic for castration resistance in men with nonmetastatic prostate cancer. Clin. Genitourin. Cancer 13(1), 10–16 (2015). https://doi.org/10.1016/j.clgc.2014.08.003

13. E. Giannetta, D. Gianfrilli, F. Barbagallo et al. Subclinical male hypogonadism. Best. Pract. Res Clin. Endocrinol. Metab. 26(4), 539–550 (2012). https://doi.org/10.1016/j.bepm.2011.12.005

14. G. Corona, C. Krausz, Late-onset hypogonadism a challenging task for the andrology field. Andrology 8(6), 1504–1505 (2020). https://doi.org/10.1111/andr.12917

15. B. Lunenfeld, G. Mskhalaya, M. Zitzmann et al. Recommendations on the diagnosis, treatment and monitoring of testosterone deficiency in men. Aging Male 24(1), 119–138 (2021). https://doi.org/10.1080/13685538.2021.1962840

16. A. Fabbri, E. Giannetta, A. Lenzi et al. Testosterone treatment to mimic hormone physiology in androgen replacement therapy. A view on testosterone gel and other preparations available. Expert Opin. Biol. Ther. 7(7), 1093–1106 (2007). https://doi.org/10.1517/14712598.7.7.1093

17. J.T. Isaacs, J.M. D’Antonio, S. Chen et al. Adaptive autoregulation of androgen receptor provides a paradigm shifting rationale for bipolar androgen therapy (BAT) for castrate resistant human. Prostate Cancer Prostate Cancer 72(14), 1491–1505 (2012). https://doi.org/10.1002/pros.22504

18. S. Denmeade, J.T. Isaacs, Bipolar androgen therapy: the rationale for rapid cycling of supraphysiologic androgen/ablation in men with castration resistant. Prostate Cancer Prostate 70(14), 1600–1607 (2010). https://doi.org/10.1002/pros.21196

19. X. Xiong, S. Qiu, X. Yi et al. Efficacy and safety of bipolar androgen therapy in mCRPC after progression on abiraterone or enzalutamide: A systematic review. Urol. Oncol. 40(1), 4.e19–4.e28 (2022). https://doi.org/10.1016/j.urolonc.2021.08.014

20. S.R. Denmeade, H. Wang, N. Agarwal et al. TRANSFORMER: A randomized phase ii study comparing bipolar androgen therapy versus enzalutamide in asymptomatic men with castration-resistant metastatic prostate cancer. J. Clin. Oncol. 39(12), 1371–1382 (2021). https://doi.org/10.1200/JCO.20.02759

21. A.M. Isidori, E. Giannetta, E.A. Greco et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin. Endocrinol. (Oxf.) 63(3), 280–293 (2005). https://doi.org/10.1111/j.1365-2265.2005.02339.x

22. A.M. Isidori, E. Giannetta, D. Gianfrilli et al. Effects of testosterone on sexual function in men: results of a meta-analysis. Clin.
23. A.M. Isidori, E. Giannetta, C. Pozza et al. Androgens, cardiovascular disease and osteoporosis. J. Endocrinol. Invest 28(10 Suppl), 73–79 (2005)

24. F. Bedussi, F. Valcamonico, A. Mosca et al. Docetaxel plus androgen deprivation withdrawal may restore sensitivity to luteinizing hormone-releasing hormone analog therapy in castration-resistant prostate cancer patients. Endocrine 54(3), 830–833 (2016). https://doi.org/10.1007/s12020-015-0827-z

25. J.T. Isaacs, W.N. Brennen, S.R. Denmeade, Rationale for bipolar androgen therapy (BAT) for metastatic prostate cancer. Cell Cycle 16(18), 1639–1640 (2017). https://doi.org/10.1080/15384101.2017.1360645

26. M.C. Markowski, M. Taplin, R. Aggarwal, et al. COMBAT-CRPC: concurrent administration of bipolar androgen therapy (BAT) and nivolumab in men with metastatic castration-resistant prostate cancer. Poster presented at the American Society of Clinical Oncology 2021 virtual annual meeting, June 4–8, 2021

27. M.T. Schweizer, R. Gulati, T. Yezefski, et al. Bipolar androgen therapy (BAT) plus olaparib in men with metastatic castration-resistant prostate cancer (mCRPC). Poster presented at the European Society of Medical Oncology 2021 annual meeting, Paris, September 16–21, 2021