Case Reports in Oncology

Case Rep Oncol 2022;15:312–317
DOI: 10.1159/000522086
Received: December 12, 2021
Accepted: January 13, 2022
Published online: March 29, 2022

Case Report

Megestrol Acetate for Heavily Pretreated Metastatic Castration-Resistant Prostate Cancer: An Old Answer for a New Problem

Maria La Vecchia[a] Daniele Galanti[b] Ivan Fazio[a] Rosario Paratore[c] Nicolò Borsellino[b]

[a]Radiotherapy Unit, Casa di Cura Macchiarella, Palermo, Italy; [b]Medical Oncology Unit, Ospedale Buccheri La Ferla Fatebenefratelli, Palermo, Italy; [c]Nuclear Medicine Department, Casa di Cura La Maddalena, Palermo, Italy

Keywords
Megestrol · Metastatic castration-resistant prostate cancer · Hormone sensitivity · Metastases-directed therapy

Abstract
Prostate cancer is the most frequent malignant tumor in male. Despite its incidence increased in the last few years, the mortality is gradually decreasing, even in patients with metastatic prostate cancer (mPC). Unfortunately, prolongation of survival leads to the exhaustion of therapeutic chances. Therefore, patients with good performance status (PS) may remain out of further active treatments. We report the clinical case of a 71-year-old patient with symptomatic metastatic castration-resistant prostate cancer (mCRPC) and good PS who progressed after multiple treatments and started a hormonal therapy with megestrol acetate (MA). MA is a synthetic progestin used for treatment of mPC in 1990s since it was shown to have an antiandrogen activity. In our case, MA managed to overcome resistance to androgen receptor-targeted agents (ARTAs), getting a dramatic biochemical and radiological response and a rapid improvement of symptoms. Our clinical case shows that MA is an interesting therapeutic option especially in long-survivor patients with mCRPC and a long progression-free survival during ARTAs therapies.

Correspondence to:
Daniele Galanti, dani.galanti@hotmail.it

Case Rep Oncol 2022;15:312–317
DOI: 10.1159/000522086

Introduction

PC is the most frequent malignant tumor in male. Recently, incidence of PC that had greatly increased in the first years of 21st century is stable, especially in the 6th decade. However, PC mortality is gradually decreasing and 5-year survival is now 91.4%, especially thanks to advances in diagnosis and treatment [1].

Also in metastatic prostate cancer (mPC), overall survival (OS) is now increasing. In the last few years, treatment of mPC has been widely revolutionized. Particularly, use of chemotherapy (docetaxel, cabazitaxel), androgen receptor-targeted agents (ARTAs) (abiraterone, enzalutamide), and radiometabolic therapy (radium-223) and combination of local and systemic treatments significatively prolonged OS of patients affected by metastatic castration-resistant prostate cancer (mCRPC). However, prolongation of survival of these patients sometimes leads to the exhaustion of therapeutic chances, despite they still have a good performance status (PS). We report clinical case of a patient with mCRPC progressing after multiple treatments, who started a hormonal therapy with megestrol acetate (MA), an old drug used for treatment of mPC in 1990s [1].

Case Presentation

In 2007, a 71-year-old Caucasian male, without significant comorbidities, was diagnosed with PC. He first presented with lower urinary tract symptoms and a high PSA (20 ng/mL). A subsequent prostatic biopsy revealed a high-grade (Gleason Score 8, 4 + 4) prostate adenocarcinoma.

From October to December 2007, patient underwent radical radiotherapy (RT), totally delivering 78 Gy to prostate and seminal vesicles and 50 Gy to pelvis. Together with RT, he started androgen deprivation therapy (ADT). PSA nadired at 0.3 ng/mL.

In October 2009, PSA reached 3.19 ng/mL. Choline PET/TC showed a local relapse with lomboaortic and interaortocaval nodal metastases, so patient underwent RT from March to April 2010. A cumulative 45-Gy dose was given to prostate and pelvic lymph nodes with a 20-Gy boost to local relapse. He had a good response and in June 2010 PSA was 0.31 ng/mL.

In December 2011, under pharmacological castration, PSA increased to 4.13 ng/mL and choline PET/TC showed left laterocervical and supraclavicular metastatic lymph nodes. From February 2012, patient started a three-weekly docetaxel chemotherapy, which continued for twelve cycles together with ADT. In December 2012, choline PET/TC showed stable disease (SD) with 2.56-ng/mL PSA. Moreover, patient received a cumulative RT dose of 46.8 Gy on metastatic lymph nodes.

His disease was stable until September 2013, when PSA raised to 9.14 ng/mL and restaging showed diffuse bone and lymph node metastases. At that time, patient also reported pelvic bone pain (VAS 6). Therefore, in January 2014 he started 1 g per day abiraterone plus prednisone 10 mg per day. Patient experienced an excellent response to abiraterone and continued it for about 3 years (January 2014–January 2017). Particularly, in May 2014 PSA became undetectable, choline PET/TC showed a complete response (CR), and pain disappeared (VAS 0).

In February 2016, because restaging showed a new symptomatic bone metastasis in right scapula with an increased PSA (2.04 ng/mL), patient underwent palliative RT (total dose 33 Gy). Subsequent PSA control dropped to 0.05 ng/mL. In September 2016, patient experienced G3 leukopenia and a G2 fluid retention with ascites and edemas, so abiraterone was reduced to 500 mg per day, with a complete recovery.

After 3 months, he reported pain on left scapula, described as a flare (VAS 9). In fact, choline PET/TC showed a CR on right scapula but revealed a new bone lesion on left humerus.

Case Rep Oncol 2022;15:312–317
DOI: 10.1159/000522086

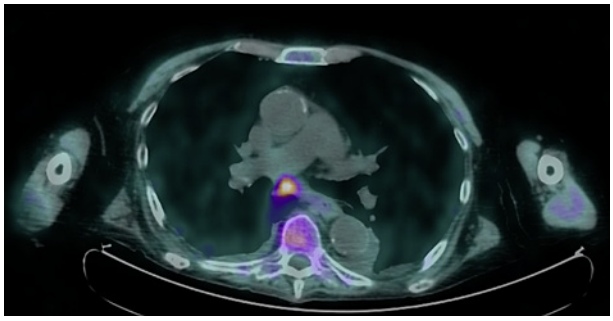

Fig. 1. Basal choline PET/TC at the beginning of MA treatment reveals progressing mediastinal nodal metastases.

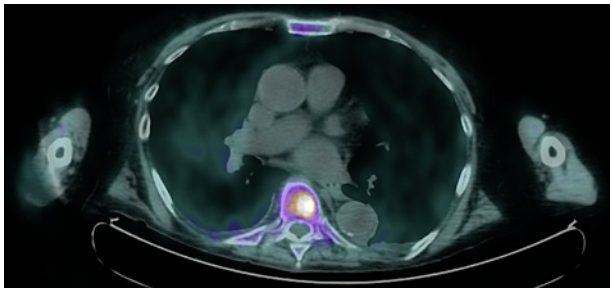

Fig. 2. Basal choline PET/TC at the beginning of MA treatment reveals appearance of new bone metastases.

Briefly, because patient refused intravenous treatments like chemotherapy or radiometabolic, from January 2017 he was treated with enzalutamide 160 mg per day and undergone 20-Gy palliative RT to left humerus. Bone pain and PSA control steadily improved.

Patient continued enzalutamide for 26 months, until March 2019. In March 2018, he underwent stereotactic RT to progressing mediastinal nodal metastases, with partial response (PR). In January 2019, enzalutamide was reduced to 120 mg per day because of G2 asthenia.

In March 2019, choline PET/TC revealed the appearance of new bone metastases in right humerus, sternum, left acetabulum, and eighth dorsal vertebra and progressive disease in left hemicostat and mediastinal lymph nodes metastases (shown in Fig. 1, 2). PSA raised to 65.72 ng/mL and patient reported severe pain in his right arm and left hip. ECOG PS declined (1). Therefore, he received palliative RT on painful bone metastases and started a new hormonal therapy with MA.

In November 2019, he showed a dramatic response with significant PSA decrease (21.26 ng/mL). Bone pain disappeared. ECOG PS improved (0). In January 2020, choline PET/TC revealed an important uptake reduction in bone metastases (shown in Fig. 3). In April 2020, after 1 year of treatment, PSA was stable (32.31 ng/mL). So, patient continued treatment with MA, without any significant toxicity.

PSA was stable until December 2020, when patient experienced a biochemical and clinical progression with a PS decline. After 20 months, patient stopped MA and then received only best supportive care. Patient died in April 2021.

Discussion

MA is a synthetic progestin that was shown to be able to lower serum concentrations of testosterone, luteinizing hormone, and follicle-stimulating hormone in patients affected by benign prostatic hypertrophy. Moreover, MA was shown to have an antiandrogen

Case Rep Oncol 2022;15:312–317
DOI: 10.1159/000522086

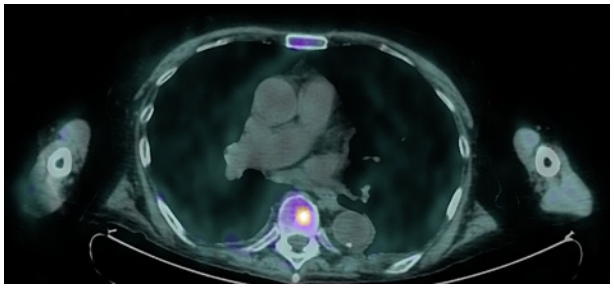

Fig. 3. Choline PET/TC after 9 months of MA treatment (January 2020) reveals an important uptake reduction in bone metastases and a metabolic CR in mediastinal nodal metastases.

activity; particularly, it blocks the binding of testosterone and dihydrotestosterone to the androgen receptor, inhibits conversion of testosterone to dihydrotestosterone by 5α-reductase, and causes adrenal suppression. In fact, dihydrotestosterone and adrenal sexual hormones are the most important endogen stimulus for promoting PC growth [2, 3].

MA was first investigated in treatment of advanced PC in late 1970s. A small study upon about 20 patients with advanced PC showed that MA is able to control disease both in untreated and pretreated patients. Better results were obviously reached in untreated. Among 11 patients pretreated with hormone therapy, one had a PR and eight SD; moreover, previous hormone treatments sometimes include estrogens. However, this study was very small and then inconclusive [4].

Subsequent studies, although small, have investigated the role of MA in the treatment of mPC, especially in hormone-refractory patients. MA has a little activity but was shown to be able to get a SD in a number of patients, even in castration-resistant disease [5–7]. These data were confirmed by a larger clinical trial, that has also demonstrated high-dose MA has not better activity and efficacy than low dose [8].

Our clinical case report deals with a patient with a very long history of mCRPC that was always characterized by a certain sensitivity to androgen-receptor blockage. In fact, after a 4-year ADT, progression-free survival with docetaxel was 18 months; of course, it is not a short period, but what was very surprising is objective response and next-line systemic treatment (NEST)-free survival with ARTAs. NEST-free survival is a new interesting endpoint that was introduced by Onal et al. [9] to evaluate real efficacy of ARTA therapies in oligoprogressing patients who received metastasis-directed therapies. Abiraterone and enzalutamide NEST-free survival was 3 years and 26 months, respectively. Abiraterone managed to get a clinical and radiological CR with a very long duration of response, while enzalutamide got a radiological PR with a significant PSA decrease.

Our clinical case also showed the importance of combining local and systemic treatments in the management of mPC to control oligoprogression sites and prolong NEST-free survival. Although this combined strategy does not represent a standard of care, several studies showed improvements in local control, progression-free survival and OS, preserving the current therapy and delaying the start of a new systemic therapy [9, 10].

Finally, after disease progression during enzalutamide, we decided to start a new line of hormone therapy. In fact, considering age, PS, and patient's will, available therapeutic options were running out, but particularly we trusted a disease's residual sensitivity to androgen receptor-targeted therapies. MA, blocking androgen receptor and adrenal hormonal synthesis, managed to overcome resistance to ARTAs, getting a dramatic biochemical and radiological response and a rapid improvement of symptoms.

Case Rep Oncol 2022;15:312–317
DOI: 10.1159/000522086

Conclusion

MA is an interesting therapeutic option for long-survivor patients affected by mCRPC, progressing after multiple lines of chemotherapy and ARTA, especially if they got a very long NEST-free survival and good response during ARTA therapies, thus suggesting a very high sensitivity to androgen receptor blocking for their disease.

Statement of Ethics

Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This retrospective review of patient data did not require ethical approval in accordance with national guidelines. Written informed consent was obtained from the patient's next of kin for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This manuscript did not receive any funding.

Author Contributions

All the authors contributed to outline and manage the diagnostic and therapeutic process of the patient. Galanti D. and Borsellino N. managed patient's medical treatments. Fazio I. and La Vecchia M. managed RT treatment. Paratore R. managed diagnostics. La Vecchia M. and Galanti D. wrote case report.

Data Availability Statement

Article's data are available from clinical documentation at Buccheri La Ferla Fatebenefratelli Hospital, Macchiarella Clinic, and La Maddalena Hospital.

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7–30.
2 Geller J, Albert J, Geller S, Lopez D. Effect of megestrol acetate (Megace) on steroid metabolism and steroid protein binding in the human prostate. J Clin Endocrinol Metab. 1976;43:1000–8.
3 Leinung MC, Liporace R, Miller CH. Induction of adrenal suppression by megestrol acetate in patients with AIDS. Ann Intern Med. 1995 Jun 1;122(11):843–5.
4 Geller J, Albert J, Yen SS. Treatment of advanced cancer of prostate with megestrol acetate. Urology. 1978 Nov;12(5):537–41.
5 Bonomi P, Pessis D, Bunting N, Block M, Anderson K, Wolter J, et al. Megestrol acetate used as primary hormonal therapy in stage D prostatic cancer. Semin Oncol. 1985 Mar;12(1 Suppl 1):36–9.

Case Rep Oncol 2022;15:312–317
DOI: 10.1159/000522086

6 Daniel F, MacLeod PM, Tyrrell CJ. Megestrol acetate in relapsed carcinoma of prostate. Br J Urol. 1990 Mar; 65(3):275–7.
7 Osborn JL, Smith DC, Trump DL. Megestrol acetate in the treatment of hormone refractory prostate cancer. Am J Clin Oncol. 1997 Jun;20(3):308–10.
8 Dawson NA, Conaway M, Halabi S, Winer EP, Small EJ, Lake D, et al. A randomized study comparing standard versus moderately high dose megestrol acetate for patients with advanced prostate carcinoma: cancer and leukemia group B study 9181. Cancer. 2000 Feb 15;88(4):825–34.
9 Onal C, Kose F, Ozyigit G, Aksoy S, Oymak E, Muallaoglu S, et al. Stereotactic body radiotherapy for oligoprogressive lesions in metastatic castration-resistant prostate cancer patients during abiraterone/enzalutamide treatment. Prostate. 2021 Jun;81(9):543–52.
10 Massaro M, Facondo G, Vullo G, Aschelter AM, Rossi A, De Sanctis V, et al. Androgen receptor targeted therapy + radiotherapy in metastatic castration resistant prostate cancer. Front Oncol. 2021;11:695136.