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CASE REPORT

Exceptional response after metronomic chemotherapy and palliative radiotherapy in castration-resistant prostate cancer: A case report

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ABSTRACT

Background: Castration-resistant prostate cancer (CRPC) has a dismal prognosis. Despite treatment, median survival of these patients is around 12-22 months.

Case Presentation: In this report, we present the case of a 71-year-old man, with CRPC and painful bone metastases treated with an association of middle-half-body radiotherapy, androgen deprivation therapy (ADT) and cyclophosphamide-based metronomic chemotherapy. Five years after palliative radiotherapy the patient is still receiving metronomic chemotherapy and ADT. He is totally asymptomatic, with undetectable PSA values and negative ^{18}F-Choline-PET/CT. The only side-effect was the development of non-insulin-dependent diabetes.

Conclusion: This treatment for its tolerability and feasibility, it could be particularly useful in older patients with CRPC. Furthermore, considering the low costs, it could be an important therapeutic option for patients living in low-resourced countries.

Keywords: Metronomic chemotherapy, radiotherapy, prostate neoplasms, CRPC, case report

Background

Prostate cancer is one of the most common diseases in industrialized countries. This tumor is usually sensitive to Androgen Deprivation Therapy (ADT) but it may finally develop into castration-resistant prostate cancer (CRPC) with median survival around 12-22 months with docetaxel-based regimens [1].

Other treatments have been introduced in clinical practice in the last years for CRPC, a tubulin-binding taxane improves overall survival (OS) in CRPC patients after docetaxel failure [2]. Abiraterone acetate is able to significantly improve OS in patients with metastatic CRPC patients with disease progression after docetaxel therapy [3]. Enzalutamide is able to prolong survival in metastatic CRPC patients [4].

External beam radiotherapy (EBRT) is frequently used in CRPC, particularly in patients with painful metastases to reduce pain and to prevent bone fractures. In these patients, the use of zoledronic acid (ZA) [5], or denosumab [6] can be an additional option to prevent skeletal-related events (SRE).

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Finally, radiometabolic therapy with Radium 223 is able to reduce SRE and improve OS in CRPC patients with bone metastases [7].

Metronomic chemotherapy (MCT) is based on continuous administration of low doses of drugs in opposition to the principle of maximum tolerated dose which is generally used in standard chemotherapy. The administration of these lower doses does not require rest periods and produces lower side effects rates. MCT has been used in the treatment of several tumors including CRPC. Cyclophosphamide is a frequently used drug in this setting because of low costs and relatively low toxicity. Here we report the case of a patient with CRPC and bone metastases. Five year after EBRT, the patient is still alive, without systemic progression of disease and with undetectable PSA.

Case Presentation

We present the case of a 71-year old patient, with prostate cancer diagnosed in October 2010 after PSA testing with a result of 20 ng/ml. He underwent multiple prostate biopsies confirming the diagnosis of prostate adenocarcinoma with Gleason Score 5+4. Clinical staging was completed with an ^{18}F-Choline PET/CT (Fig. 1a), not showing tumor sites outside the prostate.

The first therapeutic step was represented by ADT with daily Bicalutamide (50 mg) and a quarterly administration of Leuprolin acetate intramuscularly. After two months, the PSA value was 1.5 ng/ml and the patient did not show relevant side effects. However, 2 months later, the patient reported the onset of rapidly increasing lumbar pain not responsive to nonsteroidal anti-inflammatory drug. The PSA value was considerably increased, having reached the value of 11.0 ng/ml and a new ^{18}F-Choline PET/CT demonstrated the presence of lumbar spine metastases (Fig. 2a). Therefore, the patient was considered as having CRCP.

The following treatment was planned: EBRT, bisphosphonate, and MCT. The patient started with an oral daily administration 50 mg of cyclophosphamide, in association with oral dexamethasone, 0.5 mg twice a day, and 4 mg of ZA once a month. After one month of this regime, he underwent middle-half body radiotherapy on proximal femurs, pelvic bones and lumbar spine. The clinical target volume also included prostate, pelvic and lumbar aortic lymph nodes. The patient received a total dose of 15 Gy, in 3.75 Gy fraction, twice a day for 2 consecutive days. The treatment was well-tolerated and the patient developed only grade 2 diarrhea, easily controlled with oral loperamide.

One month after middle-half-body EBRT the patient reported complete resolution of lumbar pain. PSA value was significantly decreased, reaching 0.4 ng/ml. Two months later the patient underwent a new ^{18}F-Choline PET/CT, showing a complete response of intraprostatic cancer and lumbar spine metastases (Fig 1b, 2b). Treatment with ZA was interrupted after 12 doses. ADT and MCT have been continued until now.

Subsequently, the patient was evaluated every 6 months with PSA, physical examination and ^{18}F-Choline PET/CT. The PSA value was <0.01 ng/ml 6 months after EBRT, and it is still undetectable at this time, 67 months after treatment beginning. ^{18}F-Choline-PET/CT did not show any clinical relapse of the disease.

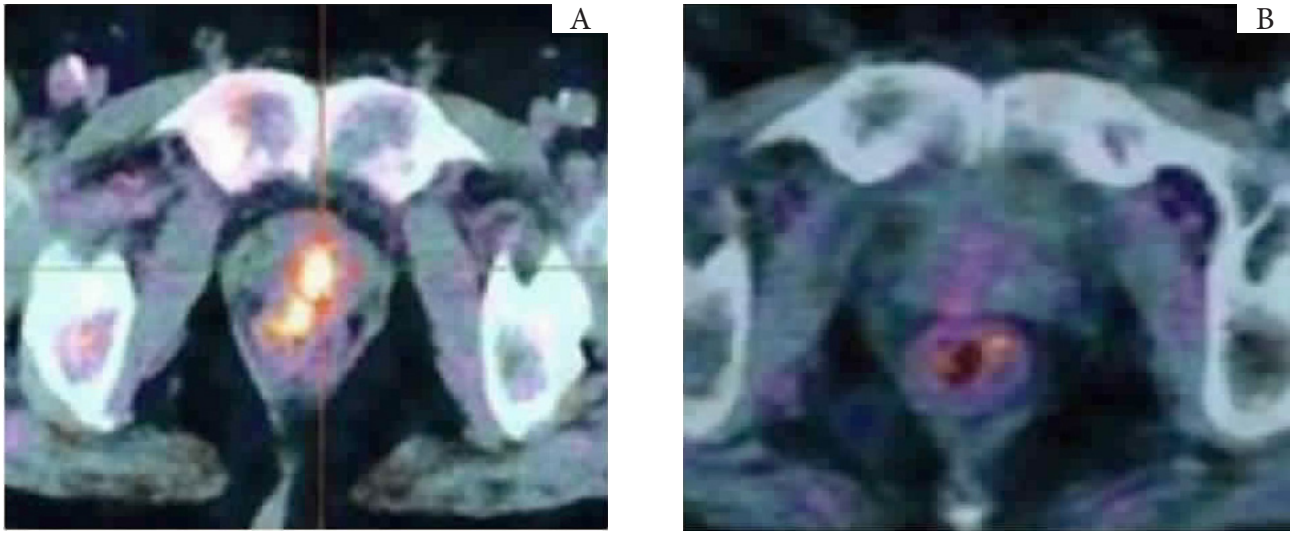

Figure 1: *^{18}F-Choline-PET/CT at prostate level;* ***(A)*** *before radiotherapy and* ***(B)*** *after radiotherapy*

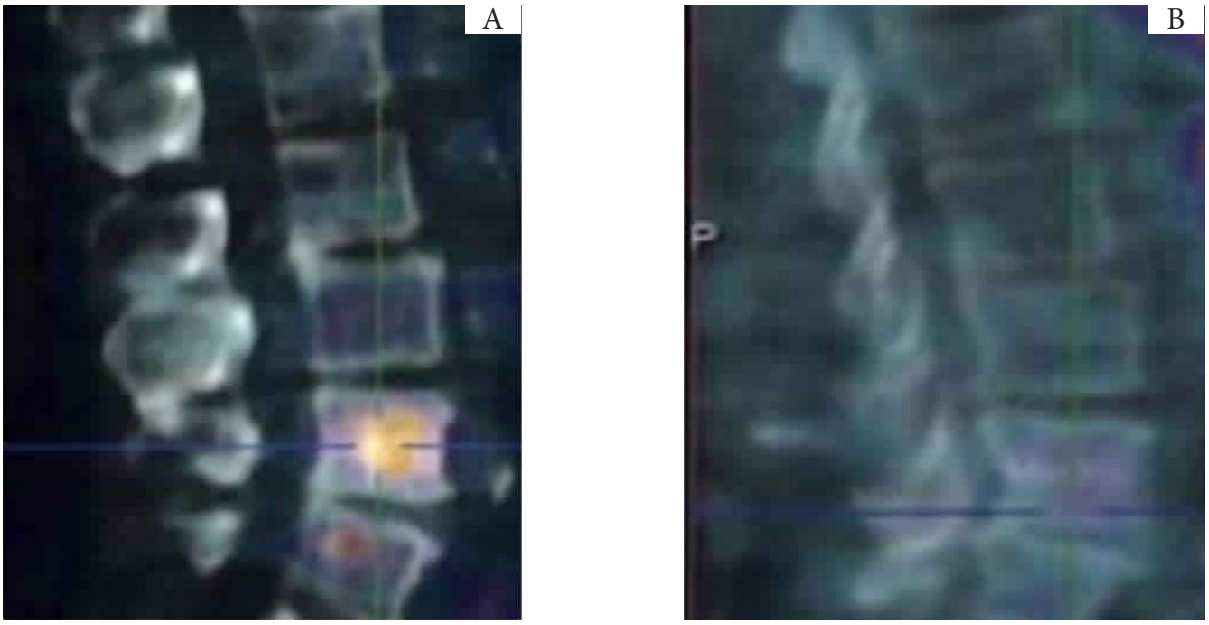

Figure 2: *^{18}F-Choline-PET/CT at lumbar spine level;* ***(A)*** *before radiotherapy and* ***(B)*** *after radiotherapy*

DISCUSSION

In this report, we described the case of a patient with CRPC and bone metastases, treated with middle-half-body EBRT and MCT based on cyclophosphamide. Sixty-seven months after treatment beginning, ^{18}F-Choline PET/CT is negative, PSA value is undetectable and the patient is totally asymptomatic. The only adverse event recorded during the treatment was the development of non insulin-dependent diabetes. An evaluation of response using PSMA-PET could have represented an interesting integration to the other information collected after the treatment but unfortunately in our country this exam is not available for clinical use.

We have to admit that some reports on long term remissions for metastatic prostatic tumor have been previously presented. However we considered this case as exceptional due to the poor prognostic features of the patient (high gleason score grade, early metastatic diffusion, early castration resistance) and the very long duration (over 5 years) of tumor response.

A literature review [8] confirmed the positive impact of this treatment. Furthermore, other studies analyzed the possibility of associating cyclophosphamide with other drugs, as celecoxib [9]. Moreover, one our previous study showed the tolerability of the association of cyclophosphamide-based MCT with EBRT in patients with non-metastatic CRPC. The results of that phase I trial also showed a 100% response rate and 19 months median time to progression [10].

The exceptional disease control observed in our patients could be attributable to combination of MCT with EBRT. In fact tumor angiogenesis can be prevented by MCT and EBRT is able to kill proliferative endothelial cells, suggesting that inhibiting angiogenesis may sensitize endothelial cells to EBRT effect.

Furthermore, targeting the vasculature may produce a paradoxical improvement of tumor oxygenation and therefore of EBRT efficacy.

However, despite the positive evidences about efficacy of this treatment, showed in retrospective studies and phase I and II studies, there is a paradoxical lack of phase III studies.

Conclusion

In conclusion, this report shows the possibility to obtain exceptionally durable results in patients with CRPC. For its tolerability and feasibility, it could be particularly useful in older patients with CRPC (or patients with relevant comorbidities).

Acknowledgements
None

List of Abbreviations

CRPC	Castration-Resistant Prostate Cancer
ADT	Androgen Deprivation Therapy
OS	Overall Survival
ZA	Zoledronic Acid
SRE	Skeletal-Related Events
MCT	Metronomic Chemotherapy
EBRT	External Beam Radiotherapy

Conflict of Interests
None

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Consent for publication
Informed consent has been obtained from the patient to present and publish this case.

Ethical approval
Yes

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Authors' contribution
Case report conception and design: AGM, MN, FM
Acquisition of data: GS, GRZ
Drafting of manuscript: RF, SC
Critical revision: FD, MF, GM
All authors approved the final version.

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References

1. Kirby RS, Fitzpatrick JM. Improved survival prospects for patients with castration-resistant prostate cancer. BJU Int. 2011;107:697-00. doi:10.1111/j.1464-410X.2010.10027.x
2. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G et al. TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376:1147-54. doi:10.1016/S0140-6736(10)61389-X
3. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, et al. COU-AA-301. Abiraterone and increased survival in metastatic prostate cancer. Investigators. N Engl J Med. 2011;364:1995-05. doi:10.1056/NEJMoa1014618.
4. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, et al. PREVAIL Investigators. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. N Engl J Med. 2014;371:424-33. doi:10.1056/NEJMoa1405095.
5. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, Chin JL, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94:1458-68.
6. Smith MR, Coleman RE, Klotz L, Pittman K, Milecki P, Ng S, Chi KN, et al. Denosumab for the prevention of skeletal complications in metastatic castration-resistant prostate cancer: comparison of skeletal-related events and symptomatic skeletal events. Ann Oncol. 2015;26:368-74.
7. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, Chodacki A, et al. ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;18;369:213-23. doi:10.1056/NEJMoa1213755.
8. Nelius T, Rinard K, Filleur S. Oral/metronomic cyclo-phosphamide-based chemotherapy as option for patients with castration-refractory prostate cancer: review of the literature. Cancer Treat Rev. 2011;37:444-55. doi:10.1016/j.ctrv.2010.12.006.
9. Fontana A, Galli L, Fioravanti A, Orlandi P, Galli C, Landi L, Bursi S, et al. Clinical and pharmacodynamic evaluation of metronomic cyclophosphamide, celecoxib, and dexamethasone in advanced hormone-refractory prostate cancer. Clin Cancer Res. 2009;15:4954-62. doi:10.1158/1078-0432.CCR-08-3317.
10. Morganti AG, Massaccesi M, Caravatta L, Macchia G, Picardi V, Deodato F, Ippolito E, et al. Radiotherapy and concurrent metronomic chemotherapy in hormone-refractory prostate carcinoma: a Phase I study. Anticancer Res. 2013;33:4585-9.

Summary of the case

Patient	1	Male , 71 year
Final Diagnosis	2	Castration-resistant prostate cancer
Symptoms	3	Lumbar pain not responsive to Nonsteroidal anti-inflammatory drug
Medications (Generic)	4	Bicalutamide (50 mg) and a quarterly administration of Leuprolin acetate intramuscularly
Clinical Procedure	5	Metronomic chemotherapy, radiotherapy
Specialty	6	Oncology
Objective	7	To treat a challenging case
Background	8	Castration-resistant prostate cancer (CRPC) has a dismal prognosis. Despite treatment, median survival of these patients is around 12-22 months
Case Report	9	In this report, we present the case of a 71-year-old man, with CRPC and painful bone metastases treated with an association of middle-half-body radiotherapy, androgen deprivation therapy (ADT) and cyclophosphamide-based metronomic chemotherapy. Five years after palliative radiotherapy the patient is still receiving metronomic chemotherapy and ADT.
Conclusions	10	This treatment for its tolerability and feasibility, it could be particularly useful in older patients with CRPC. Furthermore, considering the low costs, it could be an important therapeutic option for patients living in low-resourced countries.