Canadian Journal of Biomedical Research and Technology

Can J Biomed Res & Tech
November 2019 Vol:2, Issue:4

Italian Chronic Care Model for mCRPC Treatment with Second-Generation Antiandrogen Agents Abiraterone Acetate and Enzalutamide

Open Access **Review Article**

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Submission: November 12, 2019
Published: November 21, 2019

Abbreviations:

ADT: Androgen Deprivation Therapy;
AIOM: Italian Association of Medical Oncology;
AIFA: AgenziaItaliana del Farmaco (Italian Drug Agency);
ASL: Azienda Sanitaria Locale (Local Healthcare Company);
CRPC: Castration Resistant Prostate Cancer;
CAP: Central Authorization Procedure;
DD: Direct Distribution
GU: GazzettaUfficiale (Official Gazette);
mHSPC: High-risk metastatic Hormone Sensitive Prostate Cancer;
NSISR: New Regional Sanitary Informative System;

Abstract

The second most common oncologic disease among men is Prostate Cancer. The most aggressive form is the castration resistant subtype. For years, docetaxel was the only treatment for it showing a median prolongation of survival of 2.9 months *[1]*. In 2013 and 2014 received marketing authorization respectively Abiraterone acetate and Enzalutamide, with a different mechanism of action. They are oral formulations, available in Territorial Pharmacy Services for home administration. Because of their innovative character they have been under monitoring control for safety assurance and under risk sharing management entry agreements for a better resource allocation.

Introduction

Oncologic diseases are principal cause of death in the world *[2]*. In Italy there are approximately 400.000 new diagnosis every year, 52% among women and 48% among men. Prostate cancer is the second-most common cancer among men *[3]*. The prostate is a hormone-dependent gland in which androgen hormones testosterone and dihydrotestosterone bind to and activate the androgen receptor, initiating nuclear translocation of androgen receptor and a subsequent signaling cascade. Due to the androgen dependency of the prostate, Androgen Deprivation Therapies (ADT) have emerged as first line treatment for aggressive prostate cancer. Such therapies are effective until the point at which prostate cancer, through a variety of mechanisms including but not limited to generation of ligand- independent androgen receptor splice variants or intra-tumoral androgen production, overcome hormone deprivation. These cancers are androgen ablation resistant, clinically termed Castration Resistant Prostate Cancer (CRPC) *[4]*. An estimated 10-20% of men within 5 years after their prostate cancer diagnosis will develop CRPC *[5]*. CRPC represents the most deadly and aggressive form of prostate cancer characterized by disease progression following appropriate surgical or pharmacologic castration and can occur with or without associated metastases as nonmetastatic (nmCRPC) or metastatic CRPC (mCRPC), although nmCRPC will eventually progress to mCRPC, with greater morbidity and mortality associated with this stage of the disease *[5]*.

First-generation antiandrogens established androgen receptor blockade as a therapeutic strategy, but these therapies do not completely block androgen receptor activity. Efficacy and potency have been improved by the development of second-generation antiandrogen therapies, which remain the standard of care for patients with CRPC. Among these Abiraterone acetate and Enzalutamide. Italian Association of Medical Oncology (AIOM) guidelines reported Abiraterone and Enzalutamide in first line and second line treatment of mCRPC *(Table 1)*.This review is intended to provide a thorough overview of treatment with second-generation antiandrogen and monitoring procedures for these innovative drugs in Italy.

First Line ADT+:	Second Line ADT+:
1) Docetaxel + Prednisone	a) Abiraterone Acetate + Prednisone b) Cabazitaxel + Prednisone c) Enzalutamide
2) Abiraterone acetate + Prednisone	a) Enzalutamide b) Docetaxel
3) Enzalutamide	a) Abiraterone acetate b) Docetaxel

Table 1: AIOM guidelines for mCRPC.

Second Generation Antiandrogen Therapies

Abiraterone has been approved in 2011 by European Centralized Authorization Procedure (CAP) for treatment of mCRPC in association with prednisone or prednisolone, in case of progression after chemotherapy with docetaxel. Italian Drug Agency (AIFA) with Determination n. 927 of 04/09/2014 published in GU n. 214 of 15/09/2014, approved use of Abiraterone in association with prednisone and prednisolone also after ADT in case of chemotherapy not indicated.Last authorization is for the treatment of high-risk metastatic hormone sensitive prostate cancer (mHSPC) in association with ADT.

Enzalutamide has been approved in 2013 by CAP for treatment of mCRPC in association with prednisone or prednisolone, in case of progression after chemotherapy with docetaxel. AIFA with Determination n. 406/2016 published in GU n. 81 of 07/04/2016, approved use of Enzalutamide in association with prednisone and prednisolone also after ADT in case of chemotherapy not indicated. In contrast with androgen receptor blockade, Abiraterone and Enzalutamide cause androgen signaling inhibition by upstream blockade of androgen production *[4]*. Abiraterone acetate prevents androgen production and Enzalutamide prevents Androgen Receptor translocation into the nucleus *(Figure 1)*.

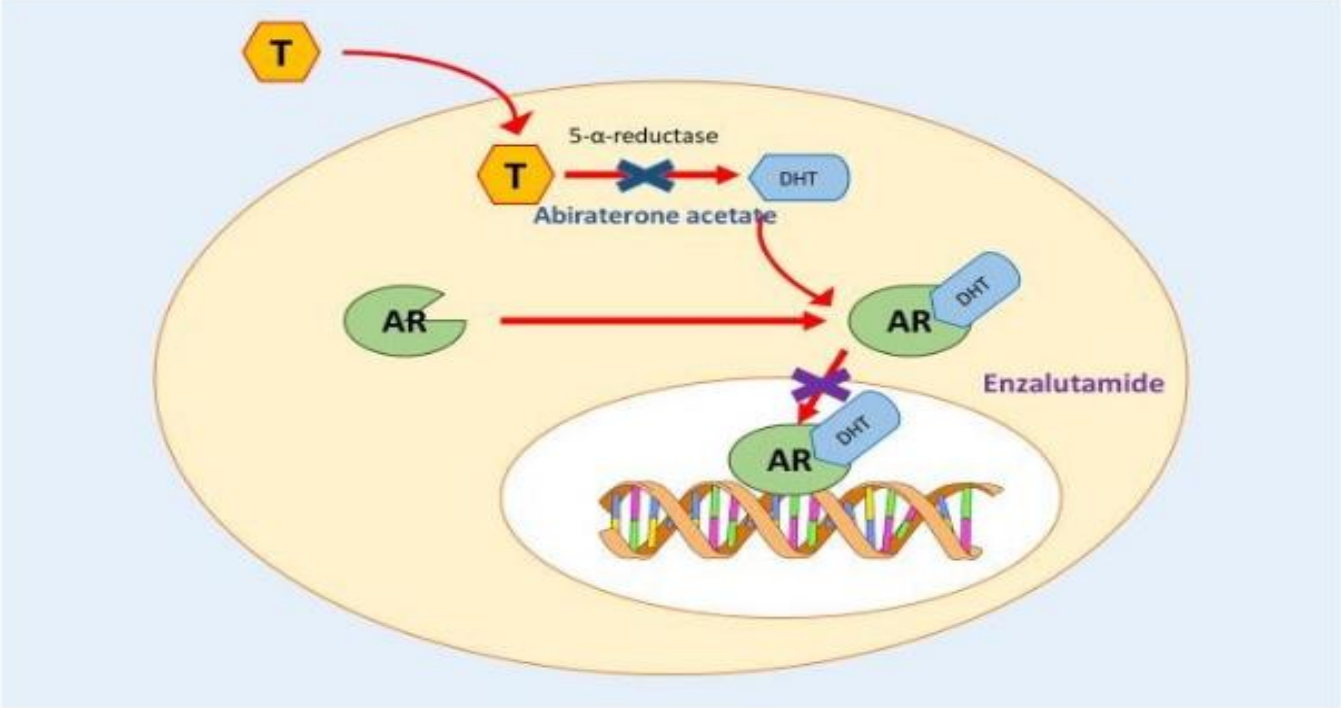

Figure 1: Schematic representation of androgen signaling cascade. Testosterone (T), produced into testes and adrenal glands, in converted into its active metabolite dihydrotestosterone (DHT) by 5-α-reducatse. DHT binds to androgen receptor (AR) and they translocate to the nucleus where they act as transcription factors. The figure shows second-generation antiandrogens mechanism: Abiraterone acetate prevents DHT biosynthesis and Enzalutamide prevents AR translocation to the nucleus.

Chronic Care Model

Abiraterone acetate and Enzalutamide are formulated for oral administration. Due to necessity of prescription by specialized doctor according to eligibility standards, and to necessity of patient's compliance in order to obtain efficacy; it has been programmed for these drugs dispensation in territorial pharmacy services. For chronic patients it has been instituted in Italy with Law n. 405 of 16 November 2001 "Direct Distribution (DD)" of domiciliary chronic treatments through ASL territorial pharmacy services, instead of traditional private pharmacies. In territorial services Hospital Pharmacist takes global charge of chronic patients becoming point of reference for specialists and also for patients. He can check respect of standard eligibility by specialists and compliance toprescription by patients. Prescription and dispensation monitoring are possible thanks to New Regional Sanitary Informative System (NSISR), a regional database instituted with Decree of Italian Ministry of Health, 31 July 2007, subsequently to conferment of monitoring tasks to AIFA with Lawn. 326 of 24 November 2003.

Monitoring Systems

In Italy Low n. 189 of 2012 established the importance of immediate availability of innovative treatments for patients. According to this law Abiraterone acetate was put in the list of innovative drugs from 06/04/2013 to 05/04/2016 *(Figure 2)*.

Agenzia Italiana del Farmaco
AIFA

ATC	PRINCIPIO ATTIVO	CLASSE	INNOVATIVITÀ	DECISIONE CTS	G.U.*	SCADENZA**
L03AX16	PLERIXAFOR	H	POTENZIALE	03/05/2011	09/12/2011	08/12/2014
L01XC11	IPILIMUMAB	H	IMPORTANTE	30/10/2012	09/03/2013	08/03/2016
L02BX03	ABIRATERONE	H	POTENZIALE	15/11/2012	06/04/2013	05/04/2016
M09AB02	COLLAGENASI DI CLOSTRIDIUM HISTOLYTICUM***	H	POTENZIALE	06/03/2013	14/03/2013	13/03/2016

Figure 2: AIFA list of innovative drugs, October 2013, in which it is mentioned Abiraterone. Drug received recognition of Innovatively by AIFA Scientific Technic consultant Committee (CTS) in 15 November 2011. It lasts in 05 April 2016. This bring to ensure availability of Abiraterone in territorial pharmacy services for mCRPC treatment.

Main difficulties in innovative drugs use come from high expense and absence of real world data of security and efficacy, so after marketing authorization AIFA programs a monitoring system to ensure therapeutic appropriateness and refunds gaining from pharmaceutical manufacturing industries. Sanitary Services and pharmaceutical manufacturing industries make Management Entry Agreements (MEAs) to share risk coming from innovative therapies. Abiraterone acetate used for treatment of mCRPC in association with prednisone or prednisolone, in case of progression after chemotherapy with docetaxel, was under Payment by Results (PbR) Agreement from April 2013 to March 2018. For the same use, Enzalutamide was under Cost Sharing (CS) agreement from December 2014 to September 2018. Abiraterone acetate and Enzalutamide used in association with prednisone and prednisolone after Antiandrogen Deprivation Therapy in case of chemotherapy not indicated were under CS agreements respectively from September 2014 to March 2018 and from April 2016 to September 2018. Pharmaceutical manufacturing industries refunds coming from MEAs are ensured by activation and maintenance of AIFA monitoring registers of treatments.

Conclusions and Future Expectations

For years, docetaxel was the only treatment for CRPC showing a median prolongation of survival of 2.9 months [1]. In 2013 and 2014 received marketing authorization respectively Abiraterone acetate and Enzalutamide, with a different mechanism of action. However, despite the initial response to second-generation agents, resistance develops in nearly all men with metastatic CRPC. Recently, a F876L missense mutation in the LBD of the AR was identified to confer resistance to Enzalutamide *[6]*, so research can never stop. Future pledge in to ensure access to care, especially innovative drugs, for all citizens, thanks to improvement of resource allocation. Moreover it is important to focus research on drugs formulation that ensure great compliance from patients. First available treatments were formulated for infusion. This, in consideration of chronic character of oncologicdisease, has a negative impact on quality of life. Innovation for second generation antiandrogens is also in formulation for oral administration. Pharmacy Services are important to ensure territorial availability of chronic therapies and adherence to prescription, from which depends efficacy of oral therapies. So great results can't be achieved only by science innovation, but also by improvement of services and contribution of healthy workers involved.

References

1. Tannock IF (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351(15): 1502-1512.
2. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics. CA Cancer J Clin 68(1): 7-30.
3. Appukkutan S, Tangirala K, Babajanyan S, Wen L, Simmons S, et al. (2019) A retrospective claims analysis of advanced prostate cancer costs and resource use. PharmacoEcomomics Open 3: 1-9.
4. Rice MA, Malhotra SV, Stoyanova T (2019) Second-generation antiandrogens: From discovery to standard of care in Castration Resistant Prostate Cancer. Front Oncol 9: 801.
5. Kirby M, Hirst C, Crawford ED (2011) Characterising the castration-resistant prostate cancer population: A systematic review. Int J ClinPract 65(11): 1180-1192.
6. Clegg NJ (2012) ARN-509: A novel antiandrogen for prostate cancer treatment. Cancer Res 72(6): 1494-1503.