Management of Anticoagulation in Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Abiraterone + Prednisone

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Background

- Abiraterone acetate is an oral, irreversible inhibitor of CYP17A1, that has been shown to be an effective agent for the management of metastatic castration-resistant and castration-sensitive prostate cancer.^{1,2,3,4}
- Abiraterone has been shown to be a strong inhibitor of CYP 2D6, CYP 2C8 and CYP 1A2, and *in vitro* data suggests moderate inhibition of CYP 3A4, CYP 2C9, CYP 2C19. Additionally, a minimal inhibitory effect on P-glycoprotein (P-gp) has been shown.^{5,6}
- A recent analysis at our institution revealed that 39% of men undergoing abiraterone+prednisone therapy used anticoagulants and/or anti-aggregatory medications.⁷
- Cancer associated thrombosis is a leading cause of death in ambulatory cancer patients receiving chemotherapy, second only to progression of disease.⁸ As a result, it is important for clinicians to provide anticoagulation options that minimize the risk of bleeding complications.⁹

Objective

- Review current literature on anticoagulation management in the oncology setting.
- Develop a management algorithm based on efficacy, safety and pharmacokinetic data to provide a point of care reference for clinicians managing patients on abiraterone + prednisone who require anticoagulation.

Methods

- A thorough review of available literature was preformed to further aid in developing the anticoagulation protocol for non-valvular atrial fibrillation and venous thromboembolism within this population.
- After reviewing the literature, a clinical framework was designed by the authors to aid clinicians in the management of those patients receiving abiraterone + prednisone concurrently with an anticoagulant.

Results

Table 1.0. Pharmacokinetics of Anticoagulants.

Agent	Target(s)	Prodrug	Bioavailability, %	Food Effect	Peak Effect	Half Life	Renal Elimination, %	Metabolic Pathway(s)	Drug Interactions
Warfarin	II, VII, IX, X	No	100	Vitamin K containing foods reduce effect	4-5 d	40h	0	CYP 2C9 (s-warfarin) CYP 3A4, 1A2, 2C19 (r-warfarin)	Many
Dabigatran	IIa	Yes	7	Delays plasma peak concentration by 2 hrs	1-3 h	14-17h	80	Liver conjugation	P-gp
Rivaroxaban	Xa	No	80	Yes (food increases bioavailability at doses of 15 & 20 mg)	2-4 h	7-11h	33	CYP 3A4, 2J2	3A4, P-gp
Apixaban	Xa	No	60	No	1-2 h	8-14 h	27	Major: CYP 3A4/5 Minor: CYP 1A2, 2C8, 2C9, 2C19, 2J2	3A4, P-gp
Edoxaban	Xa	No	62	No	1-2 h	5-11 h	50	Glucuronidation, CES1, CYP 3A4	P-gp
LMWH	Xa/IIa	No	90	No	3-4 h	3-5 h	40	Desulfation and depolymerization	Pharmacodynamic

Abbreviations: P-gp (p-glycoprotein); Xa (factor Xa); CES 1(carboxylesterase 1); IIa (thrombin); LMWH (low molecular weight heparin)

* - Monitor INR 3 days after initiation and then once weekly for 4 weeks, as INR becomes stable the interval may be increased slowly.

Figure 1.0. Anticoagulation management for atrial fibrillation in a patient receiving abiraterone + prednisone.

Abbreviations: CAD; coronary artery disease. ASA; acetylsalicylic acid. CHADS₂; congestive heart failure, hypertension, age >65, diabetes, prior stroke or transient attack. CrCl; creatinine clearance. INR; international normalized ratio.

Table 2.0. Recommended management strategies for anticoagulation in patients receiving abiraterone + prednisone.

Atrial Fibrillation:	Therapy:
CHADS ₂ Score 0 and age ≤ 65 CHADS ₂ Score 0 and CAD CHADS ₂ Score ≥ 1 and/or age ≥ 65	No anticoagulation ASA Anticoagulation with Edoxaban, Rivaroxaban or Warfarin*
Deep Vein Thrombosis/ Pulmonary Embolism	LMWH is standard of care. Rivaroxaban or Edoxaban as alternative.
Mechanical Heart Valve	Warfarin* is the only acceptable anticoagulant.

* - Close monitoring of INR

Abbreviations: ASA, acetylsalicylic acid; CAD; coronary artery disease. CHADS₂, Congestive heart failure, hypertension, age, diabetes, prior stroke or transient attack; LMWH, low-molecular weight heparin.

Conclusion/Implications

- Abiraterone + prednisone therapy has become a mainstay of the management of advanced prostate cancer, and is often used over prolonged periods of time.
- We have summarized herein a framework of how to safely use abiraterone + prednisone in men with prostate cancer on anticoagulants, applying best current knowledge.
- Evidence available to date suggests that patients with an indication for anticoagulation such as atrial fibrillation, VTE and mechanical heart valves can be treated safely with abiraterone + prednisone with appropriate monitoring.

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