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Apalutamide Induced Neutropenia: An Unusual Side Effect and a Literature Review

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Abstract

Prostate cancer is among the most frequently diagnosed cancers and a leading cause of cancer-related mortality in men worldwide. Newer generation Androgen receptor axis targeted (ARAT) has been implemented in the management of prostate cancer in both metastatic hormonal sensitive and resistant settings. It has been associated with great efficacy, well tolerability and an acceptable safety profile. We report a case of an 80-year-old male with metastatic Hormonal Sensitive Prostate Cancer (mHSPC) who developed febrile neutropenia secondary to newer generation ARAT (Apalutamide) which has completely resolved following drug interruption and short course GCSF support. To the best of our knowledge, this is the first report of apalutamide associated febrile neutropenia, literature reviewing revealed that the incidence of febrile neutropenia in patients receiving ARAT is not common and most of the febrile neutropenia in patients with prostate cancer occurs in patients receiving chemotherapy. Although this is an extremely rare adverse event caution should exercise when prescribing these drugs especially with the emerging evidence supporting the combination of ARAT's and Poly (ADP-ribose) polymerase (PARP) inhibitors.

Keywords: Apalutamide; Neutropenia; Febrile neutropenia; Prostate cancer; Androgen receptor axis targeted (ARAT) inhibitors

Introduction

Prostate cancer is among the most frequently diagnosed cancers and a leading cause of cancer-related mortality in men worldwide [1]. Carcinogenesis of prostate cancer relies on androgens for growth and progression. As such, testosterone deprivation and direct targeting of the androgen receptor are common and effective strategies in treatment [2]. Apalutamide is an inhibitor of the ligand-binding domain of the androgen receptor (AR) which showed a large impact on radiological PFS and overall survival (OS) in patients with prostate cancer. Apalutamide has been proven to increase OS in non-metastatic castration resistant prostate cancer (nm-CRPC) [3] and in mHSPC [4]. Safety analysis of these studies showed that the side effect profile was comparable to placebo and major side effect profile that leads to drug discontinuation was ranging from 8-15 % [3, 4], with only one case of neutropenia that lead to drug interruption. Neutropenia can be a life-threatening condition and is associated with many drugs including anti-cancer therapy [5, 6]. It is especially important to be cognizant of this complication in cancer patients as sepsis is common and carries a high mortality rate in this patient population

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[7]. We are reporting a rare case of apalutamide-induced neutropenia in a patient with mHSPC.

Case Presentation

An 80-year-old man with no past medical history and with no intake of medications was seen with newly diagnosed mHSPC. He was started on androgen deprivation therapy (ADT). Prostate Specific Antigen (PSA) at the time was 384.56 ug/L reference range [0.00 – 4.00], hemoglobin (HB) 110 g/L [135-175] white blood cell count (WBC) 6.4 × 10^9 cells/mm3 [4.5-11× 10^9], absolute neutrophil count (ANC) of 5.14 × 10^9 cells/mm3 [1.80-7.70× 10^9] representing 80% of the total white blood cell count, platelet count (PC) 247 ×10^9 cells/mm^3 [140 - 450× 10^9]. The patient underwent staging with computed tomography (CT) scans and bone scans which revealed no visceral metastasis and was consistent with low-risk low volume disease. He was started on apalutamide 240 mg orally once daily three weeks following ADT initiation, CBC at the time revealed (HB) 106 g/L, WBC 4.9× 10^9 cells/mm^3, ANC 3.35 × 10^9 cells/mm^3, PC 306 × 10^9 cells/mm^3. The treatment was well tolerated with no side effects. The patient had a follow up 4 weeks after initiating apalutamide, the patient reports no side effect and was tolerating the medication well, CBC at the time showed (HB) 96 g/L, (WBC) 1.6× 10^9 cells/mm^3 (ANC) of 0.97 × 10^9 cells/mm^3 representing 59% of the total white blood cell count, (PC) 197 × 10^9 cells/mm^3.

37 days following starting apalutamide the patient started to have fever reaching 39.1 degree Celsius, he reported cough and productive sputum, when arriving to the emergency department he was mildly somnolent but maintaining Glasgow coma scale (GCS) score of 14/15 [E3, V5, M6]. Laboratory work up revealed (HB) 89 g/L, (WBC) 0.3 × 10^9 cells/mm^3, (ANC) of 0.0 × 10^9 cells/mm^3 representing 0.94 % of the total white blood cell count, (PC) 223 × 10^9 cells/mm^3, (PSA) at the time was 2.12 ug/L.

CT scan showed bilateral lower lobe parenchymal opacities suspicious for pneumonia, the patient was treated as high-risk febrile neutropenia with intravenous tazobactam piperacillin and doxycycline. Blood cultures were negative. Blood smear revealed absence of WBC, no blasts or dysplastic cells, the patient was admitted to the oncology floor, apalutamide was held and was started on grastofil 300 mcg, ANC recovered in 5 days following these measures to 0.77. 3 weeks following his hospital admission his neutrophils recovered to baseline without recurrence of neutropenia, it was decided upon discussion with the patient to continue with ADT alone.

Discussion

Fever in febrile neutropenia is defined as 38.3 º or higher or sustained elevation of temperature 38.0 and higher for one hour [8]; Severe neutropenia is defined as ANC less than < 0.5 x 10^9/L or expected to be severely neutropenic in the next 48 hours [8], it represents one of oncology true emergency due to previously high mortality rate [9, 10]. In HSPC setting the reported incidence of febrile neutropenia ranges from 6-30% [11-15], which is markedly higher than the rate of 3% demonstrated in the castrate-resistant phase [16], all these cases were in patients receiving chemotherapy.

Apalutamide is a new generation (ARAT) inhibitor that has regulatory approval to be used in mHSPC and nmCRPC [3, 4]. ARATs work by inhibiting the binding of androgen-to-androgen receptor (AR), nuclear translocation of the androgen–AR complex, and binding of AR transcription complex to DNA-binding sites and transcription elements. The AR plays an essential part in the pathogenesis of the disease and remains a key therapeutic target even in castration resistant disease [17-20].

Apalutamide demonstrated its superiority in both settings as shows in two phase III trials. At a median follow up of 52 months in the SPARTAN trial apalutamide significantly improved overall survival reaching 73.9 months vs 59.9 compared to placebo in nmCRPC [3]. In patients with mHSPC median OS was not reached vs 52.2 months despite 39.5% patient cross over to apalutamide arm at median follow-up of 44.0 months in the TITAN study [4].

About 1611 patient was treated with apalutamide in both studies (including cross over patients), with a median duration of treatment at least 30 months in patient started on apalutamide upfront and 15 months in patient who had crossed over from placebo, there was only one patient in the TITAN study who required dose interruption due to febrile neutropenia [3, 4] [Table 1].

Other Bone marrow adverse events such as anemia were slightly higher in the placebo group 13.7% compared to the treatment group (13.2%) [4], there was no mention of any bone marrow toxicity documented in SPARTAN trial [3], there was no record of any grade of thrombocytopenia in either of the studies.

The risk was similar also in other newer generations ARAT such as darolutamide, as the risk of neutropenia was similar in both groups receiving docetaxel in combination with ARAT or placebo (39.3% and 38.8%, respectively) [21]. Cases of neutropenia and other bone marrow toxicities have been documented with other ARAT's and were ranging from 1-2% in patients receiving enzalutamide [24-30]. The estimated risk of neutropenia in Abiraterone + prednisone / prednisolone (AAP) ranges from 2-7%, grade ¾ and febrile neutropenia was only 1% [12, 31-36] [Table 1].

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Table 1: Showing different newer generation ARAT in phase III trials, rate of neutropenia and other bone marrow toxicity.

Study	ARAT	Settings	Comparison arm	Rate of neutropenia	Rate of other bone marrow toxicity				
SPARTAN study [3]	Apalutamide	mHSPC	Placebo	No data mentioned	No data mentioned				
TITAN study [4]	Apalutamide	nmCRPC	Placebo	No clear data, however, rate of neutropenia that led to dose Interruption was 0.4% and febrile neutropenia was 0.2 %, rate of neutropenia that led to dose reduction was 0.2%	Anemia 13.2% in apalatumide and 13.7% in placebo No data mentioned for thrombocytopenia				
ARASENS study [21, 22]	Darolutamide	mHSPC	Compared Darolutumide + Docetaxel with Placebo + Docetaxel	39.3% in the darolutumide + docetaxel group and 38.8% in placebo + Doecetaxel group.	Anemia was 27.8% in the darolutumide + docetaxel group and 25.1% in the Placebo + Doecetaxel group. No data mentioned for thrombocytopenia				
ARAMIS study [23]	Darolutamide	nmCRPC	Placebo	No data mentioned	Rates of anemia were 5.6 % in the treatment group vs. 4.5% in the placebo group. No data mentioned for thrombocytopenia				
ENZAMET study[24]	Enzalutamide	mHSPC	Compared Enzalatumide with or without docetaxel vs. SOC + with or without Docetaxel	Adverse event / Arm	Febrile Neutropenia	Neutropenia	Adverse event / Arm	Thrombocytopenia	Anemia
				SOC + Docetaxel	12.8%	8.8%	SOC + Docetaxel	0.008%	16.8%
				SOC alone	0%	0.006%	SOC alone	0.006%	6%
				Enzalutumide + Docetaxel	13.7%	13.7%	Enzalutumide + Docetaxel	0%	17.3%
				Enzalutumide alone	0.003%	1.6%	Enzalutumide alone	0.006%	6.1%
ARCHES study[25]	Enzalutamide	mHSPC	Placebo	1.4 % in the enzalutumide group and 0.7 % in placebo group.	Thrombocytopenia rates were similar across all groups 0.5%				
PREVAIL study[26]	Enzalutamide	mCRPC	Placebo following progression on chemotherapy	1.6 % in the enzalutumide group and 0.6 % in the placebo group.	No data mentioned				
PROSPER study[27]	Enzalutamide	nmCRPC	Placebo in chemotherapy naïve patients	1 % in the enzalutamide group and < 1 % in the placebo group.	Thrombocytopenia rates were similar across all groups about 1% No mention of anemia the trial and supplementary index				
AFFIRM study [28, 29]	Enzalutamide	mCRPC	Placebo following progression on chemotherapy	No data mentioned	Rate of anemia is 14.4 % in the treatment arm compared to 19 % in the placebo arm.				
PRESITE study[30]	Enzalutamide	mCRPC	Following progression on Enzalutumide in mCRPC Docetaxel was added for 10 cycles and continuing of enzalutumide was allowed in a subgroup vs. placebo	34 % in both groups, with similar rate of Grade 3 and above adverse event	Rate of anemia is 20 % in the treatment arm compared to 12 % in the placebo arm. No mention of thrombocytopenia the trial.				

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PEACE-1 study[31]	AAP	mHSPC	SOC vs. SOC + Abiraterone / SOC + Docetaxel + Abiraterone vs. SOC + Docetaxel	Rate of febrile neutropenia was 0.9% in SOC + abiraterone group compared to 0.4% in the SOC group. Rate of febrile neutropenia was 5.2% in SOC with docetaxel + abiraterone group compared to 5.4% in the SOC + docetaxel group.	No data mentioned
LATITUDE study[32]	AAP	mHSPC	Placebo	Neutropenia 4-5% in treatment group vs 2-4% in the placebo group,	Rates of thrombocytopenia were 7% in the treatment group vs. 3-4% in the placebo group. Rates of anemia were 11% in the treatment group vs. 14-15% in the placebo group
STAMPEDE study [12, 33]	AAP	mHSPC / non metastatic locoregionally advanced prostate cancer iwith prostate radiotherapy	Multi-arm multi-stage study including ADT alone vs ADT + Abiraterone + Prednisolone + ADT + Docetaxel + Prednisolone	Neutropenia 7% in ADT + AAP vs 4% in the ADT group, Rates of febrile neutropenia were 0% in both arms In a sperate analysis the rate of febrile neutropenia in ADT + AAP was 1% compared to 17% in ADT + Docetaxel	Rates of thrombocytopenia were 5% in the treatment group vs. 3% in the SOC group. Rates of anemia were 46% in the treatment group vs. 35% in the SOC group
COU-AA-301 study [34]	AAP	mCRPC following progression on docetaxel	Placebo	Neutropenia 1 %, febrile neutropenia <1% compared to placebo < 1% and 0 % respectively	Rate of thrombocytopenia was similar (4%), rates of anemia was higher in the placebo group 28% compared to 25% in the abiraterone group
COU-AA-302 study [35, 36]	AAP	mCRPC, in chemotherapy naïve patients	Placebo	No data mentioned	No data mentioned

Conclusion

To our knowledge this is the first case of apalutamide induced neutropenia, although the incidence of such adverse event is rare, it's a serious adverse event and with the presence of other causes of neutropenia in patients with prostate cancer this may be a future dilemma especially with the emerging evidence to support the use of dual therapy of ARAT and PARP inhibitors in patients with mCRPC [37-41].

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Conflicts of Interest

The authors declare no conflict of interest.

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