Febrile Neutropenia (FN) rates in Metastatic Hormone Sensitive Prostate Cancer: The Role of Antibiotics as Primary Prophylaxis

Lara Pemberton[1]*, Kenrick Ng[2,3]*, Ursula McGovern[1,3], Alan Macdonald[2] ,Hasti Barot[3], Myria Galazi[2,3], Peter Wilson[2], Paula Wells[2], Mark Linch[3], Constantine Alifrangis[2,3]‡, Jonathan Shamash[2]‡

1. Department of Medical Oncology, Barnet General Hospital
2. Department of Medical Oncology, St Bartholomew's Hospital
3. Department of Medical Oncology, University College London Hospital

* Joint First Authors

‡ Joint Senior Authors

Correspondence to Kenrick Ng: kenrickng@doctors.org.uk, +447928693663, Cancer Institute, University College London, Paul O'Gorman Building, 72 Huntley Street, Bloomsbury, London, UK.

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The STAMPEDE and CHAARTED trials established docetaxel as first-line treatment alongside androgen deprivation therapy (ADT) in patients with metastatic hormone-sensitive prostate cancer (mHSPC). However, this treatment regimen is associated with a considerable risk of febrile neutropenia (FN). The CHAARTED trial reported FN rates of 6%[1] whereas STAMPEDE demonstrated a FN rate of 15%[2]. Both were significantly higher than the rate of 3% exhibited in the castrate-resistant setting[3]. Real-world studies have demonstrated FN occurrences up to 30%[4-6], prompting calls to use granulocyte colony stimulating factor (GCSF) as primary FN prophylaxis; which is costly and associated with a range of side effects.

We investigated the effectiveness of prophylactic fluoroquinolones as primary FN prophylaxis in mHSPC. We concurrently explored the contribution of maintenance prednisolone to FN, as steroids are immunosuppressive[7] and the treatment regimens in the two landmark trials differed in the use of maintenance prednisolone.

Data from 159 mHSPC patients from three large healthcare trusts in London, UK who commenced docetaxel chemotherapy between January 2015 and February 2018 were retrospectively collected. They were divided based on their supportive care regimens. Cohort A (n=81) received up to six cycles of docetaxel 75mg/m^2 every 3 weeks alongside ADT + concomitant prednisolone 5mg BD, consistent with the STAMPEDE regimen. Cohort B (n=78) received docetaxel + ADT in a similar fashion but without steroids (consistent with CHAARTED) and with prophylactic ciprofloxacin 500mg BD between days 5-15 of each cycle of treatment. In both cohorts, dose reductions and delays were implemented at the treating oncologist's discretion. Prophylactic GCSF was not administered routinely. In all three centers, it was at the clinician's discretion to administer docetaxel at 60mg/m^2 for the first cycle to assess tolerance. In St Bartholomew's Hospital, which constituted most of the patients in Cohort B, the default setting on the prescribing system was to

initiate docetaxel at 60mg/m^2 to assess tolerance but this increased by default to 75mg/m^2 in Cycle 2.

The two groups were balanced in age (median age in cohort A, 68 years vs cohort B, 67 years), Gleason score (GS ≥8; 80.2% in cohort A vs 82.0% in cohort B) and proportion who completed 6 cycles of treatment (87.6% in cohort A vs 88.4% in cohort B). There was a significant difference in starting dose (82.1% in cohort B vs 41.0% in cohort A started at 60mg/m^2). The time from commencing ADT to commencing docetaxel was comparable between the two groups (Cohort A: Median 49 days, Interquartile Range: 34-68 days, Cohort B: Median 63 days, Interquartile Range: 35-80 days).

The rate of any Grade 3/4 adverse event was 17.2% in Cohort A and 12.8% in Cohort B (p=0.57). Importantly, the incidence of FN was significantly higher in cohort A, which received maintenance prednisolone and did not receive prophylactic antibiotics (14.8% vs 2.5%, p=0.006).

Due to the significant difference in FN rates between the two cohorts, we studied patient and disease factors which may influence onset of FN. (Table 1)

In cohort A, where 12 (14.8%) of patients developed FN, the majority of them (9/12, 75%) did so following cycle 1. 8/12 (66.7%) received 75mg/m^2 at their first cycle. In cohort A, 16 patients received prophylactic GCSF: 3 as primary prophylaxis (3.7%) and 13 (16%) as secondary prophylaxis. The reason for primary prophylaxis was not documented for two of the patients, whilst the other was previously treated for a haematological malignancy. Of the 13 who received secondary prophylaxis, one of them did not have FN but was admitted with Klebsiella septicaemia after cycle 1.

In cohort B, where 2 (2.5%) patients developed FN, one received full dose at their first cycle, while the other started at 60mg/m^2. Neither received prophylactic GCSF, although the latter received a 25% dose reduction after developing FN at cycle 3 (at a dose of 75mg/m^2).

The time from ADT to docetaxel was also evaluated in both groups, as a short interval has been associated with a higher incidence of FN[4]. No significant difference was observed in the subpopulation which experienced FN from the time from ADT to docetaxel in the total cohort.

Importantly, in cohort B, where prophylactic ciprofloxacin was used for 10 days, there were no documented cases of Clostridium Difficile recorded in any of the 78 patients, as of August 2019.

The low incidence of FN (2.5%) in cohort B prompts discussion. This is likely to be a combined effect of prophylactic ciprofloxacin and omission of prednisolone, although it is difficult to assess the relative contribution of each approach. An indirect comparison of the FN rates in STAMPEDE (15%) vs CHAARTED (6%) suggests that prednisolone is likely to play a role. The lower starting dose (60mg/m^2) in cohort B may explain the differences observed in incidence of FN after cycle 1. However, nearly all patients in cohort B (70/73, 95.8%) received a dose escalation to 75mg/m^2 in cycle 2 and hence this is unlikely to influence cumulative FN rates across six cycles (Figure 1).

While the use of GCSF as primary prophylaxis for FN is the more popular choice, a systematic review of breast cancer patients treated with docetaxel highlighted that antibiotics were non-inferior to GCSF[8], while recognizing cost implications and different toxicity profiles.

Many clinicians express concern that the use of prophylactic antibiotics will encourage colonization with antibiotic-resistant organisms. In a trial of myeloma patients, the use of prophylactic quinolones demonstrated no evidence of increased colonization with antibiotic-resistant organisms or incidence of healthcare associated infections[9]. There are also fears about Clostridium difficile infections, but our results, in tandem with previous studies, show no evidence that the use of prophylactic ciprofloxacin increases the risk of diarrhea associated with this organism[10].

In this multicenter retrospective audit, the addition of prophylactic ciprofloxacin and omission of maintenance prednisolone is associated with a decreased risk of developing FN. We demonstrate that this supporting regimen is a cost-effective alternative to primary GCSF prophylaxis, and often associated with less toxicity. We suggest that this supportive care schedule be considered to mitigate the high rates of FN associated with chemohormonal treatment in mHSPC.

		Cohort A (n=81)	Cohort B (n=78)
Documented Febrile Neutropenia		12 (14.8%)	2 (2.5%)
Time from commencing ADT to commencing docetaxel	Median (days)	49	63
	Range (days)	13-361	7-123
	IQR (days)	34-68	35-80
Use of GCSF in Total Cohort	Primary Prophylaxis	3	0
	Secondary Prophylaxis	13	0
Proportion Commencing with Docetaxel 60 mg/m^2		34 (41.0%)	73 (82.1%)
Proportion Requiring Dose Reduction from 75mg/m^{2*}		18 (22.2%)	10 (12.8%)
Proportion Who Remained at Docetaxel 60mg/m^2 throughout		3 (3.7%)	3 (3.8%)
Proportion Completing 6 cycles		71 (87.6%)	69 (88.4%)
Starting Doses of Patients who Developed FN	Total number of patients	n = 12	n = 2
	Full Dose (75mg/m^2)	8	1
	Starting dose of 60mg/m^2	4	1
Time of Developing FN in Patients who Developed FN	First Cycle	9	1
	Subsequent Cycles	3	1

Table 1: Baseline Characteristics of Patients in Cohort A (n=81) and Cohort B (n=78). Table also denotes starting doses and time of incidence of FN in Cohort A (n=12) and Cohort B (n=2) in patients who developed febrile neutropenia. *Patients who started on 60mg/m^2 and remained at this dose were not considered in this analysis. ADT = Androgen Deprivation Therapy, FN = Febrile Neutropenia, GCSF = Granulocyte Colony Stimulating Factor, IQR = Interquartile Range,

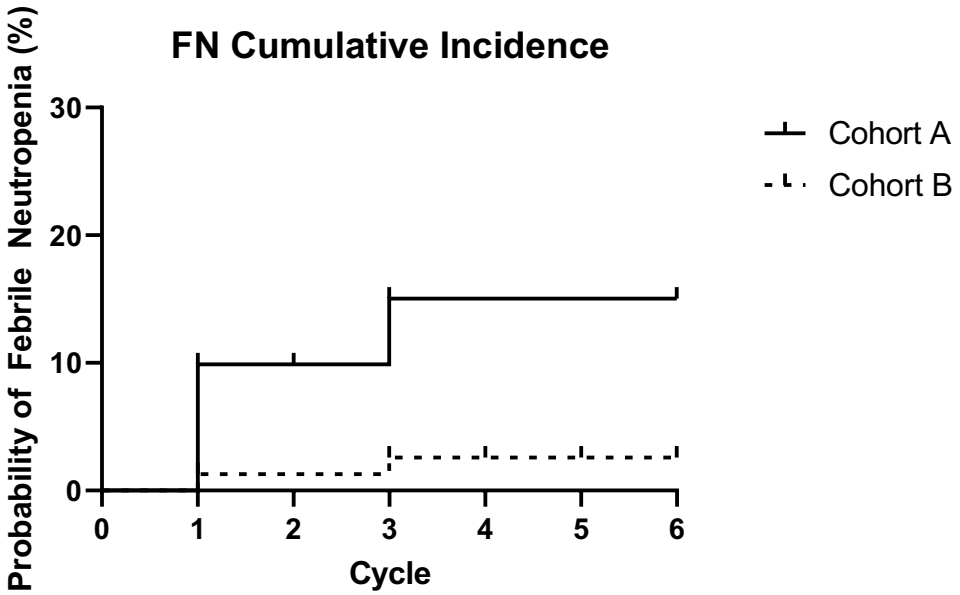

Figure 1: Cumulative Incidence Plot showing proportion of patients who experienced febrile neutropenia after each cycle of treatment. Patients who did not complete the six cycles of treatment are censored at the annotated cycles of treatment. FN = Febrile Neutropenia

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Authors' contributions

- **Conception and Design:** Constantine Alifrangis, Jonathan Shamash, Kenrick Ng, Paula Wells, Ursula McGovern, Mark Linch
- **Data Acquisition:** Lara Pemberton, Kenrick Ng, Alan Macdonald, Hasti Barot, Myria Galazi
- **Data Analysis and Interpretation:** Lara Pemberton, Kenrick Ng, Alan Macdonald, Myria Galazi, Constantine Alifrangis, Ursula McGovern, Jonathan Shamash
- **Drafting Manuscript**: Lara Pemberton, Kenrick Ng
- **Statistical Analysis:** Kenrick Ng, Peter Wilson

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